SYMPTOM-BASED DEPRESSION SUBTYPES AND SEX: A MIXTURE MODELING APPROACH INTEGRATING BIOPSYCHOSOCIAL ASPECTS

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by Stephanie Alexandra Rodgers

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on the Recommendation of the Doctoral Committee:
Prof. Dr. phil. Martin grosse Holtforth (main advisor)
PD Dr. phil. Vladeta Ajdacic-Gross
PD Dr. phil. Christoph Flückiger

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“Taxonomy is described sometimes

as a science and sometimes as an art, but really it’s a battleground”

— Bill Bryson (2003, p. 319) —

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ABSTRACT

Major depressive disorder (MDD) is a highly heterogeneous psychopathological construct that risks subsuming different types of psychiatric conditions. A possibility in order to deal with this lack of specificity is to define more homogeneous depression subtypes, such as symptom-based subtypes (Baumeister & Parker, 2012). Mixture modelling (e.g., latent class analysis (LCA) and latent transition analysis (LTA)) displays a promising person-centered statistical approach enabling the extraction of homogeneous subgroups of depressed subjects. Prior mixture modelling studies have derived typical (also referred to as melancholic), atypical, and moderate depression subtypes, which were not only discriminable by differing symptom profiles, but also by specific biopsychosocial characteristics. However, despite the well-established impact of sex on depression there is still a lack of knowledge about empirically derived sex-related and sex-specific depression subtypes to date. In particular, population-based studies examining this issue are required. The present doctoral thesis aimed to contribute to this research gap by three studies providing the basic research for future advances fostering the effectiveness and specificity of depression treatment.

In the first study (manuscript I), the stability and transition patterns of the three empirically derived symptom-based subtypes severe typical, severe atypical, and moderate depression were examined over the time span of 20 years using data from the Zurich Study. LTAs under consideration of the predictor sex were fitted to population-based data of 322 subjects manifesting depressive symptoms. Subjects with temporally stable depressive phenomenology were furthermore characterized by psychosocial characteristics. Results indicated that the severe atypical subtype and the moderate subtypes displayed a high temporal stability, which even increased over time, whereas stability of the severe typical subtype was relatively low. The latter was associated with male sex, while females were more prone to belong to the severe atypical subtype. This study was the first to detect relevant sex-related differences in long-term stability and transition patterns of depression subtypes. Males exhibited a more pronounced stability of depression subtypes than females. In contrast, females displayed more transitions between the depression subtypes over time; transitions from the severe typical to the severe atypical subtype and vice versa were particularly prominent. With regard to the psychosocial characteristics, both stable severe subtypes showed significant associations with psychosis syndromes, while eating disorders were only significantly associated with the stable severe atypical subtype.

The second study (manuscript II) aimed at replicating the empirically found depression subtypes from the first study by applying LCAs to another cross-sectional community sample including subjects with depressive symptoms (373 males; 443 females). The ZInEP (German: ***Z****ürcher* ***I****mpulsprogramm zur* ***n****achhaltigen* ***E****ntwicklung der* ***P****sychiatrie)* survey was parallelised regarding sex-age composition to the longitudinal cohort used in study one. Additional sex-specific depression subtypes were expected due to the higher statistical power of the large database. This study successfully replicated the severe male-related typical subtype, the severe female-related atypical subtype, and the non-sex-related moderate subtype. Furthermore, two male-specific depressive subtypes were derived: a large severe irritable/angry-rejection sensitive (IARS) subtype, partly resembling Rutz's male depressive syndrome (Rutz, 1999; Rutz, von Knorring, Pihlgren, Rihmer, & Walinder, 1995) and a small psychomotor retarded subtype. With regard to associated psychosocial characteristics, there were similarities and discrepancies between the sexes. Males with membership in the severe typical subtype displayed the lowest masculine gender role orientation, while typical depressed females revealed more anxiety disorders. The severe atypical subtype was markedly associated with eating disorders in both sexes, however only in females with substance use (alcohol and drugs). In contrast, substance use was linked to the severe IARS subtype in males. Compared to the stable, long-term depression subtypes of study one, the comorbidity patterns of the depressive subtypes in the cross-sectional study were much more pronounced. This may be the result of 'switchers' fluctuating between typical and atypical episodes (and perhaps further depressive subtypes) over time, which could only be captured in the longitudinal study design. The author proposes that the issue of 'switchers' has been underestimated in depression research to date.

Finally, the third study (manuscript III) accounted for a biological characterisation of the data-driven depression subtypes from study two by comparing the available gonadal hormones of 60 depressive males with 15 healthy subjects. Both the severe typical subtype and severe IARS subtype showed significantly higher serum testosterone levels compared to the controls. The lower testosterone concentration of the severe atypical subtype was obviously confounded by the high body mass index (BMI) associated with this subtype.

Overall, the empirically derived depression subtypes under consideration of the factor sex are replicable in both cross-sectional and longitudinal samples and are quite well characterizable by

biopsychosocial correlates, supporting the assumption that MDD consists of several homogeneous, etiopathogenetic conditions. Combining the new data-driven findings with the existing paradigms and theories has the potential for innovative inspiring perspectives. The extended knowledge on symptom-based depression subtypes may provide the basic research for future preventions and more specific depression treatments.

ZUSAMMENFASSUNG

Die depressive Störung *major depressive disorder* (MDD) ist ein psychopathologisches Konstrukt, welches sich durch ein hohes Mass an Heterogenität auszeichnet und damit das Risiko birgt, unterschiedliche psychiatrische Entitäten zu subsummieren. Die Definition von homogeneren Depressionssubtypen ist eine Möglichkeit, diesem Mangel an Spezifität zu begegnen (Baumeister & Parker, 2012). Mischverteilungsmodelle, wie latente Klassenanalysen (*Latent Class Analysis*, LCA) und latente Transitionsanalysen (*Latent Transition Analysis*, LTA), sind vielversprechende, personenzentrierte statistisches Verfahren, anhand derer homogene Subgruppen von depressiven Personen abgeleitet werden können. Frühere Studien mit solchen statistischen Modellen fanden Evidenz für typische (auch bekannt als melancholische), atypische, und moderate depressive Subtypen, die neben ihren unterschiedlichen Symptomprofilen auch durch spezifische biopsychosoziale Korrelate charakterisierbar waren. Obschon viel über den Einfluss des Faktors Geschlecht auf die Depression bekannt ist, gibt es nach wie vor Wissenslücken hinsichtlich der empirisch abgeleiteten, geschlechtsassoziierten und geschlechtsspezifischen Depressionssubtypen. In diesem Zusammenhang sind insbesondere Allgemeinbevölkerungsstudien vorteilhaft. Die vorliegende Doktorarbeit wendet Mischverteilungsmodelle auf depressive Symptome in der Allgemeinbevölkerung an und liefert damit die notwendige Grundlagenforschung um diese Wissenslücken zu reduzieren, sodass die Effektivität und Spezifität zukünftiger Depressionsbehandlungen verbessert werden kann.

In der ersten Studie (Manuskript I) wurde die Stabilität und die Übergangsmuster der drei empirisch abgeleiteten, symptombasierten Depressionssubtypen schwer belastet typisch, schwer belastet atypisch und moderat über den Zeitraum von 20 Jahren anhand der Zürich-Studie untersucht. LTAs unter Berücksichtigung des Prädiktors Geschlecht wurden an Allgemeinbevölkerungsdaten von 322 Personen mit depressiven Symptomen angewendet. Diejenigen Personen, die eine zeitlich stabile depressive Phänomenologie aufwiesen, wurden zusätzlich anhand von psychosozialen Korrelaten charakterisiert. Die Ergebnisse zeigten, dass der schwer belastete atypische und der moderate Depressionssubtyp die höchste zeitliche Stabilität aufwiesen – welche über die Zeit hinweg sogar noch anstieg –, während die Stabilität des schwer belasteten typischen Subtyps geringer ausfiel. Letzterer war mit dem männlichen Geschlecht assoziiert, während Frauen häufiger eine atypische Depression aufwiesen. Diese Studie deckte damit erstmalig relevante geschlechtsspezifische

Unterschiede in der longitudinalen Stabilität und den Übergangsmustern von Depressionssubtypen auf. Männer wiesen insgesamt eine höhere Stabilität der depressiven Subtypen auf als Frauen. Frauen hingegen zeigten mehr Übergänge zwischen den Depressionssubtypen, dabei waren Wechsel zwischen dem schwer belasteten typischen Subtyp und dem schwer belasteten atypischen Subtyp und vice versa besonders prominent. Hinsichtlich der psychosozialen Charakteristiken zeigten beide schwer belasteten Depressionssubtypen signifikant mehr Assoziationen mit psychotischen Syndromen, während Essstörungen signifikant mit dem stabilen, schwer belasteten atypischen Subtyp assoziiert waren.

Mit der zweiten Studie (Manuskript II) wurde beabsichtigt, die in der ersten Studie empirisch gefundenen Depressionssubtypen zu replizieren. Dazu wurden LCAs an einer weiteren Allgemeinbevölkerungsstichprobe im Querschnitt durchgeführt. Alle Personen mit depressiven Symptomen wurden eingeschlossen (373 Männer; 443 Frauen). Die Studie aus dem ***Z****ürcher* ***I****mpulsprogramm zur* ***n****achhaltigen* ***E****ntwicklung der* ***P****sychiatrie* (ZInEP) war hinsichtlich der Geschlechts-Alter Zusammensetzung mit der Längsschnittstudie aus Manuskript I parallelisiert. Aufgrund der höheren statistischen Power wurden zusätzliche, geschlechtsspezifische Depressionssubtypen erwartet. Diese Studie replizierte sowohl den mit dem männlichen Geschlecht assoziierten, schwer belasteten typischen Subtyp, wie auch den mit dem weiblichen Geschlecht assoziierten, schwer belasteten atypischen Subtyp, und den geschlechtsunabhängigen, moderaten Subtyp. Zusätzlich wurden zwei weitere, spezifisch männliche Depressionssubtypen gefunden: ein schwer belasteter *severe irritable/angry-rejection sensitive* (IARS) Subtyp, welcher die grösste Gruppe von Männern beinhaltete und teilweise Rutz's *male depressive syndrome* glich (Rutz, 1999; Rutz et al., 1995) und ein kleiner, psychomotorisch retardierter Subtyp. In Bezug auf die Assoziationen mit psychosozialen Charakteristika gab es Ähnlichkeiten und Unterschiede zwischen den Geschlechtern. Männer mit dem schwer belasteten typischen Subtyp wiesen die tiefste maskuline Geschlechterrollenorientierung auf, während die schwer belasteten typisch depressiven Frauen mehr Angststörungen zeigten. Der schwer belastete atypische Subtyp war bei Frauen mit Substanzgebrauch (Alkohol und Drogen) sowie bei beiden Geschlechtern deutlich mit Essstörungen assoziiert. Im Gegensatz dazu war Substanzgebrauch bei den Männern mit dem schwer belasteten IARS Depressionssubtyp assoziiert. Im Vergleich zur ersten Studie waren die Komorbiditätsmuster der Depressionssubtypen viel ausgeprägter. Dies könnte durch Personen zu erklären sein, welche im Laufe der Zeit zwischen typischen und atypischen Episoden (und möglicherweise weiteren Depressionssubtypen) hin- und her wechseln (sog. *switcher*) – ein Phänomen, das ausschliesslich im

longitudinalen Studiendesign zum Vorschein kam. Die Autorin nimmt an, dass diese Wechsel zwischen den Depressionssubtypen in der bisherigen Depressionsforschung unterschätzt wurden.

In der dritten Studie (Manuskript III) wurde eine biologische Charakterisierung der in Manuskript II gefundenen Depressionssubtypen vorgenommen. Dazu wurden die gonadalen Hormone von 60 depressiven Männern mit 15 gesunden männlichen Kontrollpersonen verglichen. Die beiden Depressionssubtypen schwer belastet typisch und schwer belastet IARS wiesen signifikant höhere Serum Testosteronwerte auf als die Kontrollen. Die tiefe Testosteronkonzentration des schwer belasteten atypischen Subtyps war aber durch den hohen *body mass index* (BMI) dieser Gruppe konfundiert.

Die drei Studien legen nahe, dass die empirisch abgeleiteten Depressionssubtypen im Querschnitt und im Längsschnitt replizierbar sind und ziemlich gut durch biopsychosoziale Korrelate charakterisiert werden können. Dies unterstreicht die Annahme, dass die MDD verschiedene, in sich homogene ätiopathogenetische Erkrankungen beinhaltet. Die Kombination der neuen datenabgeleiteten Befunde mit den vorherrschenden Paradigmen birgt das Potential für innovative inspirierende Perspektiven. Das hier erweiterte Wissen hinsichtlich der symptombasierten Depressionssubtypen könnte die Grundlagen für die künftige Prävention und spezifischere Behandlung der Depression liefern.

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1. Introduction

1.1 Thesis outline

The major aim of the present doctoral thesis was to gain a more detailed insight into empirically derived sex-related and sex-specific symptom subtypes, their longitudinal stability and transition patterns, and their associations with biopsychosocial characteristics. For this purpose mixture modelling was applied, a promising statistical approach in order to extract homogeneous subgroups of subjects.

The present doctoral thesis was conducted within the scope of the Epidemiology subproject of the Zurich Program for Sustainable Development of Mental Health Services (ZInEP; German: ***Z****ürcher* ***I****mpulsprogramm zur* ***n****achhaltigen* ***E****ntwicklung der* ***P****sychiatrie*). The Epidemiologic Survey was designed by PD Dr. phil. Vladeta Ajdacic-Gross from the Department of Public Mental Health at the Zurich University Hospital of Psychiatry in order to generate comprehensive data about mental health and disorders in the general population of adults in the Canton of Zurich, Switzerland. The cross-sectional study methodologically parallels the longitudinal Zurich Study by Prof. Jules Angst (Angst, Dobler-Mikola, & Binder, 1984; Angst et al., 2005). In the current thesis, a selection of data from the ZInEP survey and the Zurich Study was analysed.

This original research including three studies was intended to provide the basis for future prevention and help to improve the effectiveness of the treatment of depression. The following broader questions furnish the wider framework of the present doctoral thesis:

- *Can the empirically derived symptom-based depression subtypes be replicated in different samples, and secondly, can they be replicated both cross-sectionally and longitudinally?*
- *Which kind of sex-related and sex-specific symptom-based depression subtypes can be empirically derived? How do they correspond with the existing psychopathological constructs and theories?*
- *Are the empirically derived symptom-based depression subtypes characterized by biopsychosocial correlates?*
- *Is mixture modelling a convenient statistical approach in order to examine symptom-based depression subtypes?*

The first section of the thesis outlines the theoretical background in which the current thesis is embedded and closes with the main research objectives. The second section contains the original research with two published and one submitted studies. Finally, the third section briefly summarizes the main interlinked findings and discusses them in a broader context, also addressing the above-mentioned questions.

1.2 Classification and definition of depression

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is the standard classification system of mental disorders, published by the American Psychiatric Association. Recently, the fifth edition of this multiaxial classification system was released (APA, 2013). The DSM is purely descriptive without providing a basic explanatory understanding of the pathogenesis of the specific mental disorder (Frances, 2013). According to DSM-5, depressive disorders can be differentiated as follows: disruptive mood dysregulation disorder, major depressive disorder (MDD) (single episode; recurrent episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder.

The diagnosis of MDD can be further characterized by its level of severity (mild, moderate, severe), the existence of psychotic features, and its illness course (partial remission, full remission, unspecified). Moreover, the addition of the following nine specifiers is available in order to clarify diagnosis: with anxious distress, with mixed features, with melancholic features, with atypical features, with mood-congruent psychotic features, with mood-incongruent psychotic features, with catatonia, with peripartum onset, with seasonal pattern. The DSM-5 criteria for a diagnosis of MDD include five (or more) symptoms, with at least one of the core features 1) or 2) present in the same two-week period: 1) depressed mood, 2) diminished interest or pleasure in activities, 3) significant weight loss/gain or decreased/increased appetite, 4) insomnia or hypersomnia, 5) psychomotor agitation or retardation, 6) fatigue or loss of energy, 7) feelings of worthlessness or excessive or inappropriate guilt, 8) diminished ability to think or concentrate, or indecisiveness, 9) recurrent thoughts of death, recurrent suicidal ideation or attempt or plan. These symptoms must persist for most of the day and occur nearly every day. They must differ from the subject's usual state, lead to significant distress or functional impairment and should not be attributable to a substance or

medical condition or to be better explained by a psychotic disorder. Finally, an earlier or current manic or hypomanic episode must be excluded (note: wording of criteria was simplified by the author). In sum, the current classification of major depression is deduced from the presence of a specific number of symptoms, which need to persist over a certain time period and beyond that lead to considerable impairment.

1.3 Epidemiology of major depressive disorder (MDD)

Major depression is a common mental disorder affecting more than 350 million people worldwide. This disorder is the major psychiatric contributor to the global burden of disease (WHO, 2012). Epidemiological U.S. data from the National Comorbidity Survey found a 12-month prevalence of 10.3 per cent (%), and a lifetime prevalence of 16.6-17.1% for MDD (Kessler et al., 2005; 1994). For Europe, the European Study of the Epidemiology of Mental Disorders (ESEMeD) (Alonso et al., 2004) found a lifetime prevalence of 12.8% MDD and the European College of Neuropsychopharmacology (ECNP)/ European Brain Council (EBC) report (Wittchen et al., 2011) reported a MDD 12-month prevalence of 6.9%, leading to an estimated 30.3 million subjects suffering from this mental disorder. Hence, MDD is the most common single mental disorder, together with specific phobia (Alonso et al., 2004). In terms of the disability adjusted life years (DALY; computed as number of years lost due to ill-health, disability, or early death), assessing the overall disease burden, unipolar depression held the highest rank, with a rate of 103.7/10'000. The DALY rate was particularly high among females (134.4/10'000), while the rate for males was nearly half as high (70.9/10'000) (Wittchen et al., 2011). This sex difference was also reflected by female/male risk ratios around 2:1 (Alonso et al., 2004; Kessler, 2003). The higher prevalence, incidence and morbidity risk of MDD occurs at mid-puberty and persists through adult life (Piccinelli & Wilkinson, 2000). A recent review however revealed an inverse sex-ratio in pre-puberty showing that boys aged <=12 years are significantly more likely to suffer from MDD than girls (Douglas & Scott, 2014).

1.4 Current explanatory model of MDD

The currently most prominent explanatory model of MDD is the vulnerability-stress model. This theoretical model assumes that predisposing genetic and social factors contribute to an increased vulnerability, which can be accentuated or reduced by psychological, social or biological development processes (Beesdo-Baum & Wittchen, 2011). The following figure illustrates this theoretical assumption (Fig. 1).

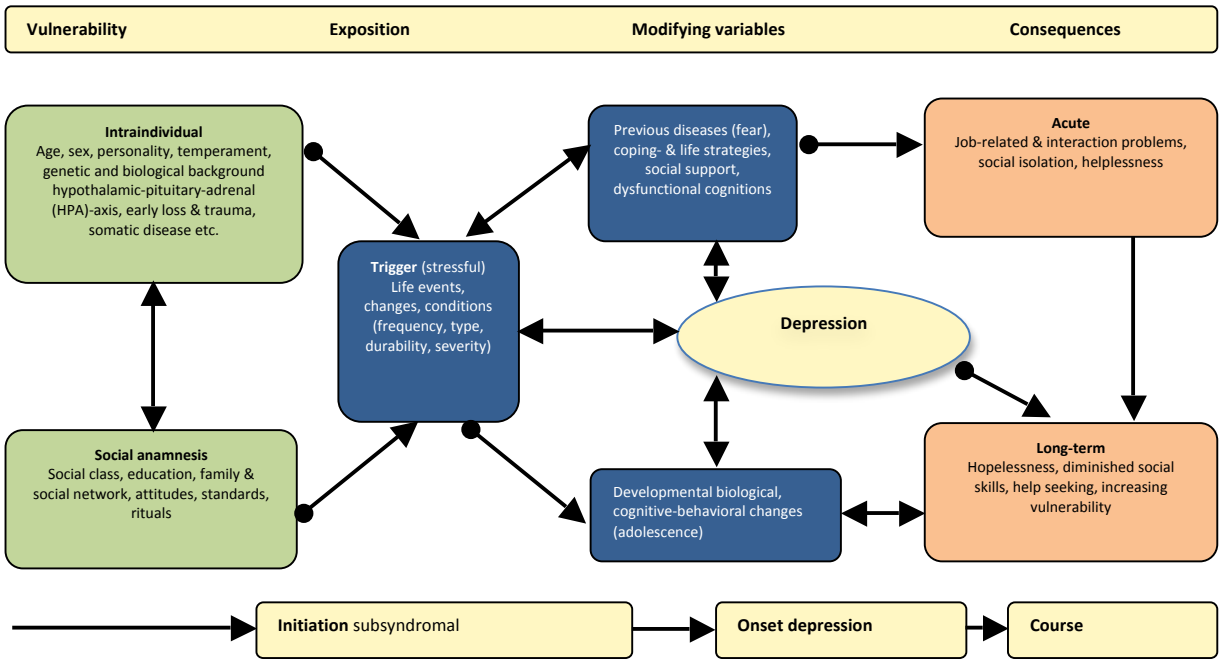

Figure 1. Conceptual aetiology model of depression according to Beesdo-Baum & Wittchen (2011), translated by the author.

The vulnerability-stress model is embedded in the biopsychosocial perspective, which was offered as a new paradigm by George Engel (1977) in the late 1970s. The biopsychosocial paradigm was claimed as alternative to the prevailing biomedical model, which was becoming an increasingly dogmatic cultural imperative. The latter had dominated industrialized societies since the mid-20th century and conceptualized disease (including mental disease) as a deviation from the norm of measurable biological (somatic) variables, without considering psychosocial and behavioural aspects of illness. This idea of mental pathology containing discrete disease entities, each with its own pathophysiology, goes back to the German psychiatrist Emil Kraepelin (1856–1926) (van Praag, 2010). Engel criticized the reductionistic principle of the biomedical paradigm, the monistic

philosophic view deriving complex phenomena from a single principle, and the doctrine of the mind-body dualism separating the mental from the somatic (which is popularly, but perhaps inaccurately traced to Descartes; Borrell-Carrio, Suchman, & Epstein, 2004; Brown, 1989; Damasio, 1994). Parallel to the biological reductionism, a psychoanalytic orthodoxy had arisen in the 20th century, resulting in severe conflicts between these schools (Ghaemi, 2006). In his biopsychosocial model, Engel proposed a new understanding of suffering, disease and illness by integrating multiple levels of organizations, from the societal to the molecular. Moreover, he emphasized the patient's subjective experience as crucial contributor to diagnosis, health outcomes and human care. To summarize, the biopsychosocial model integrates both a philosophy of clinical care and a practical clinical guide (Borrell-Carrio et al., 2004).

1.5 Criticism concerning the construct of MDD

1.5.1 Raised concerns

After two decades of extensive research considering MDD, dissatisfaction has arisen with this construct (Baumeister & Parker, 2012; Ghaemi, 2008; Luyten, Blatt, Van Houdenhove, & Corveleyn, 2006; G. Parker, 2005; G. Parker, 2006). As Baumeister and Parker (2012) noted, there are 227 possible symptom constellations of a MDD diagnosis according to DSM-IV (APA, 2000), and increasing evidence demonstrates that this highly heterogeneous construct risks subsuming or 'homogenising' constituent types of disease conditions. The validity of the MDD construct was further questioned by inconsistent neurobiological and genetic findings (I. Antonijevic, 2008; I. A. Antonijevic, 2006; Krishnan & Nestler, 2010; Shyn & Hamilton, 2010), and inconsistency with respect to the efficacy of psychopharmacological- and psychotherapies (Baumeister, Hutter, & Bengel, 2011; Cuijpers, van Straten, Bohlmeijer, Hollon, & Andersson, 2010; Ghaemi, 2008; Kirsch et al., 2008; Pigott, Leventhal, Alter, & Boren, 2010; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008). As a consequence, the conceptualization of more homogeneous depression subtypes of MDD were advanced (for meta-review see Baumeister & Parker, 2012). Such subgroups, as recently shown by interpersonal subtypes, bear the potential to foster personalized psychotherapy (Grosse Holtforth et al., 2014).

1.5.2 Diagnostic 'splitting' versus 'lumping': An historical embedding going back to the turn of the twentieth century

Two German psychiatrists significantly influenced the classification of depression. At the end of the nineteenth century, Emil Kraepelin simplified and refined his earlier depression nosology by collapsing all abnormal mood syndromes into one single category, which was labelled 'periodic insanity' (*das periodische Irresein,* 1896) and later 'manic-depressive insanity' (*das manisch-depressive Irresein,* 1899) (Kraepelin, 1893, 1971; Mondimore, 2005). In contrast to this unitary conceptualization of depression, Kurt Schneider (1887–1967) introduced a binary model by coining the terms endogenous depression and reactive depression in 1920 (Schneider, 1920). In other words, the 'lumping' view postulated a unitary depressive disorder, while the 'splitting' view separated depression into different disorders.

An analogous development as described in Europe proceeded in North America and the United Kingdom. Influential British academics, e.g., Eysenck (1970), Kendell (1976) and Mapother (1926) debated for decades about the unitary/binary debate, without however obtaining a clear resolution (G. Parker, 2005).

Based on this background, a small group of U.S. psychiatrists developed specific diagnostic criteria for 15 mental disorders, including major depressive disorder, to enhance communication between clinicians and researchers and to standardize psychiatric diagnoses (Feighner et al., 1972). These criteria are also known as the 'Feighner criteria'. In 1978, Spitzer et al. (1978) refined and expanded the 'Feighner criteria' into the Research Diagnostic Criteria (RDC), which were included in the DSM-III, published two years later (APA, 1980). In fact, the etiologically atheoretical DSM-III was almost an international revolution in the nosology of mental disorders by implementing research findings, more precise criteria, and coding quantifications, thereby overcoming the psychoanalytic jargon and 'psychobiological' concepts (Alarcon, 2009; G. Parker, 2009).

Hence, the dominant current diagnostic model is unitarian, conceptualizing depression as a single, dimensional condition, merely varying by its severity (Baumeister & Parker, 2012; G. Parker, 2000). However, besides the unitarian/binarian view, Klein (1974) proposed a third option postulating multiple depressive disorders (G. Parker, 2000). Based on findings regarding response to

monoamine oxidase inhibitors (MAOIs), Klein and his group from the U.S. Columbia University created the DSM-IV concept of atypical depression (Angst et al., 2006). This and further symptom-based depressive subtypes will be illustrated in the subsequent section.

1.6 Symptom-based MDD subtypes

1.6.1 Common symptom subtypes: melancholic (aka typical), atypical, and psychotic depression

The three symptom-based subtypes melancholic (also referred to as typical)-, atypical-, and psychotic depression are considered as MDD specifiers in DSM. The key features of these subtypes are presented in Table 1.

MDD Specifier	
Melancholic	A. Either of the following, occurring during the most severe period of the current episode: (1) loss of pleasure in all, or almost all, activities (2) lack of reactivity to usually pleasurable stimuli (does not feel much better, even temporarily, when something good happens) B. Three (or more) of the following: (1) Distinct quality of depressed mood (i.e., the depressed mood is experienced as distinctly different from the kind of feeling experienced after the death of a loved one) (2) depression regularly worse in the morning (3) early morning awakening (at least 2 hours before usual time of awakening) (4) marked psychomotor retardation or agitation (5) significant anorexia or weight loss (6) excessive or inappropriate guilt
Atypical	A. Mood reactivity B. Two (or more) of the following features: Significant weight gain or increase in appetite, hypersomnia, leaden paralysis (i.e. heavy, leaden feelings in arms or legs), long-standing pattern of interpersonal rejection sensitivity (not limited to episodes of mood disturbance) that results in significant social or occupational impairment C. Criteria are not met for With Melancholic Features or With Catatonic Features during the same episode.
Psychotic	Presence of either delusions or hallucinations Mood-congruent features: e.g., delusions of guilt, nihilistic delusions, somatic delusions, delusions of poverty, auditory hallucinations Mood-incongruent features: persecutory delusions, delusions of thought insertion, delusions of thought broadcasting, delusions of control

Table 1. Key features of three MDD specifiers, adapted and summarized from (APA, 2000).

A large amount of research has been conducted in order to characterize the symptom-based subtypes melancholia, psychotic, and atypical depression by biopsychosocial correlates (e.g., Angst et al., 2006; I. A. Antonijevic, 2006; Leventhal & Rehm, 2005; G. Parker et al., 2010; Thase, 2009). It was demonstrated that these subtypes were quite discriminable by core biological correlates. For example, the hypothalamic–pituitary–adrenal (HPA) axis (also referred to as stress axis which is dysregulated during MDD (I. Antonijevic, 2008)) led to *hyper*cortisolemia in melancholic and psychotic depression and to diametrically differing *hypo*cortisolemia in atypical depression (Baumeister & Parker, 2012; Mondimore, 2005; Posternak, 2003; Quitkin & Davies, 2004; Thase, 2009). In contrast, the findings regarding the psychosocial correlates are more inconclusive. Merely rejection sensitivity has been consistently found within subjects showing an atypical depressive phenomenology (Angst et al., 2006; G. Parker et al., 2002; G. B. Parker & Thase, 2007).

Above and beyond the biopsychosocial characteristics, hypotheses concerning the efficacy of subtype-specific treatments are available for all three symptom-based subtypes (Baumeister & Parker, 2012). However, in terms of depression with mood-congruent psychotic symptoms, some authors proposed that this symptom cluster does not depict a separate diagnostic entity, but rather a more severe occurrence of depression (Maj, Pirozzi, & Di Caprio, 1990).

1.6.2 Sex-related symptom subtypes

In order to explain the higher overall prevalence of MDD in females, a large number of risk factors have been examined. These include psychological (e.g. sexual abuse), hormonal (e.g. premenstrual, pregnancy, perimenopause, menopause), neurochemical (e.g. HPA axis), anatomic (e.g. volume reductions in the prefrontal cortex and hippocampus), genetic (e.g. copies of the S allele in the serotonin promoter gene region), and personality factors (e.g. ruminative coping style) (Grigoriadis & Robinson, 2007). However, the exact determinants of sex-differences in MDD are far from being established (Piccinelli & Wilkinson, 2000). Some research has attributed the female preponderance of MDD to the higher prevalence of certain symptom-based subtypes. In this context, atypical-, anxious-, and somatic depression were postulated as female-preferred subtypes (Halbreich & Kahn, 2007). Aside from depressive features, the anxious subtype was characterized by symptoms such as moderate to severe worrying, psychic anxiety, somatic anxiety, subjectively experienced anger, depersonalization or derealization and negative self-evaluation (Clayton et al., 1991). Yet the

findings concerning the characterization by biopsychosocial correlates have been judged as too unspecific to delineate this phenomenology as a separate depressive subtype (Baumeister & Parker, 2012). The somatic subtype was described by symptoms such as depression, sleep disturbances, fatigue, anxiety and diverse aches and pain (Silverstein, 1999, 2002; Silverstein et al., 2013). However, the concept of somatic depression has not been included in the DSM classification system to date. These female-preferred depression subtypes may derive from distinct etiologies and pathophysiological mechanisms. In this context, the role of gonadal hormones including their interaction with other hormonal systems (e.g. (HPA) axis) and neurotransmitters has been discussed (Halbreich & Kahn, 2007).

Whereas female-associated subtypes of depression were intensively examined, the male-related phenomenological expression of depression received less consideration, particularly outside the U.S. (Möller Leimkühler, Bottlender, Strauss, & Rutz, 2004). However, a male-related depressive syndrome was proposed by Rutz et al. (1999; 1995). Besides the core depressive symptoms, the male depressive syndrome considers symptoms such as irritability, restlessness, loss of self-control, alcohol or substance abuse and overworking (Zierau, Bille, Rutz, & Bech, 2002). The scale assessing this syndrome was developed in the context of an educational program for general practitioners that took place on the Swedish island of Gotland (Rutz, 1999; Rutz et al., 1995; Walinder & Rutz, 2001). A number of studies have validated the Gotland Scale (Bech, 2001; Innamorati et al., 2011; Möller Leimkühler, Heller, & Paulus, 2007; Zierau et al., 2002). Two studies showed that this scale captured depression in both sexes (Innamorati et al., 2011; Möller Leimkühler & Yucel, 2010), and consequently does not distinguish a sex-specific depressive syndrome. The psychometric reliability and validity of this measure has been doubted (Magovcevic & Addis, 2008). In particular, the need for a validation of this scale in unbiased community samples and specified with respect to differential diagnosis was emphasized (Möller Leimkühler et al., 2007). Up to date, no study investigating data-derived depression symptom subtypes has included Rutz's male depressive syndrome. Moreover, the aspect of gender role orientation has so far been neglected within the framework of symptom-based subtypes, despite masculine gender role orientation seeming to be a protective factor against depression (Helgeson, 2005). Gender role orientation conceptualizes a personality trait that an individual develops as a member of a social system in which certain attributes are stereotyped as masculine or feminine (Williams & Best, 1982).

In sum, a growing body of research indicates that the depression symptom phenomenology shows considerable sex disparity. Nevertheless, there is a lack of evidence for sex-related and sex-specific depression subtypes from population-based samples.

1.6.3 Course stability as validity criterion

As Kendell (1974) emphasized in his classic paper, an important aspect of the usefulness of a conceptualized subtype is provided by its temporal stability. Unfortunately, very few studies have focused on this specific topic. The findings regarding the melancholic subtype are rather inconsistent, which could be the result of various conceptualizations of this subtype, including concepts such as endogenous and typical depression (Baumeister & Parker, 2012; Melartin et al., 2004). In contrast, stability of the severe atypical subtype was higher and consistently confirmed by population-based studies (G. Parker, 2009), clinical samples (Nierenberg, Pava, Clancy, Rosenbaum, & Fava, 1996), and genetic data of an epidemiological survey (Kendler et al., 1996). Finally, studies examining the psychotic subtype provided high stability data (Charney & Nelson, 1981; Helms & Smith, 1983). Unfortunately, all these longitudinal depression studies did not consider sex, despite this factor being fundamentally involved in depression.

1.6.4 Gonadal hormones as biological correlate

Gonadal hormones influence brain systems and other hormonal systems such as the HPA axis, which is known to be changed in subjects with major depression (Young & Korszun, 2010). Three well-known gonadal hormones are testosterone, estrogen and progesterone. The effects of estrogen on the regulation of mood, behaviour, and cognition and the dysphoric effects of progesterone are well documented in females (Halbreich & Kahn, 2007). In this context, pubertal stage, hormonal shifts such as postpartum period and a cycle-dependent vulnerability were the focus of research (Kuehner, 2003). With regard to testosterone, associations between low testosterone levels (hypogonadism) and depression have been found in males (Joshi et al., 2010; Schweiger et al., 1999; Shores, Moceri, Sloan, Matsumoto, & Kivlahan, 2005; Shores et al., 2004). However, some studies demonstrated that this association particularly refers to certain depressive subpopulations such as males with dysthymia or minor depression (Berglund, Prytz, Perski, & Svartberg, 2011; Johnson, Nachtigall, & Stern, 2013; Seidman et al., 2002; Shores, Kivlahan, Sadak, Li, & Matsumoto, 2009). Moreover, a

growing body of evidence suggests that there is a nonlinear association between testosterone levels and depressive symptoms and that both low and high testosterone levels are associated with depression and even hypomania/mania (Booth, Johnson, & Granger, 1999; Johnson et al., 2013; Kouri, Lukas, Pope, & Oliva, 1995; Malone, Dimeff, Lombardo, & Sample, 1995; Pope & Katz, 1994; Pope, Kouri, & Hudson, 2000; Su et al., 1993; Talih, Fattal, & Malone, 2007). However, these results stem from studies examining the effect of exogenous testosterone administration on affective symptoms. In contrast, the associations between elevated endogenous testosterone levels and affective symptoms remain unclear up to date. Due to the fact that the body mass index (BMI) is negatively correlated with testosterone (Zitzmann & Nieschlag, 2001), this confounding variable needs to be further considered in such analyses.

1.7 Person-centered mixture modeling approaches

Accumulating evidence from data reducing techniques supports the existence of symptom-based MDD subtypes (Carragher, Adamson, Bunting, & McCann, 2009; Eaton, Dryman, Sorenson, & McCutcheon, 1989; Kendler et al., 1996; Lamers, Burstein, et al., 2012; Lamers et al., 2010; Sullivan, Kessler, & Kendler, 1998; Sullivan, Prescott, & Kendler, 2002). In contrast to variable-centered statistical methods (e.g., regression analysis, factor analysis, and structural equation modeling), which focus on relationships among variables in order to predict outcomes, person-centered approaches (e.g., cluster analysis, and latent class analysis (LCA)) focus on relationships among individuals and aim at grouping individuals into homogeneous categories. In this manner, unobserved population heterogeneity can be captured by qualitatively or quantitatively differing subpopulations (i.e. latent classes) (Lubke & Muthén, 2005; B. Muthén & Muthén, 2000). Two examples for person-centered analysis are LCA and latent transition analysis (LTA), also referred to as mixture modelling.

1.7.1 Latent Class Analysis

The primary goal of LCA is to find the smallest number of latent classes that describe the associations among a set of observed categorical variables (or indicators). The latent classes are represented by categorical latent variables. Within LCA, the classes are increased stepwise until the

best model fit is achieved (B. Muthén & Muthén, 2000). The most commonly used model fit indices are the Akaike information criterion (AIC) (Akaike, 1987), the Bayesian information criterion (BIC) (Schwarz, 1978), the sample-size adjusted BIC (ABIC) (Sclove, 1987), and the entropy measure (K. L. Nylund, Asparouhov, & Muthén, 2007). LCA can be only applied to cross-sectional data (B. Muthén & Muthén, 2000).

LCAs including both sexes have modelled melancholic (author's note: melancholic depression is often synonymously labelled 'typical' in LCA studies) and atypical depression (Baumeister & Parker, 2012). However, only two LCA studies have performed separate LCAs by sex (Alexandrino-Silva et al., 2013; Crum, Storr, & Chan, 2005) to date, although the impact of sex on depression is well-established (Möller Leimkühler et al., 2004).

1.7.2 Latent Transition Analysis

Whereas LCA examines class membership in cross-sectional data, LTA depicts its longitudinal extension. LTA, also referred to as hidden Markov modelling, explores change in categorical latent classes over time. Based on the interindividual response pattern to manifest items, homogeneous subgroups (latent classes) of individuals are extracted. At each time of measurement, a latent class model (LCA) is postulated, and stage-sequential development is summarized in transition probability of latent classes over two serial times. LTA considers the change in class membership over time by estimating the probability of a transition from a class at one time point to a class at the next time point. Apart from transition patterns, LTA also allows the investigation of stability among subtypes (B. Muthén & Muthén, 2000; L. K. Muthén & Muthén, 1998-2012; K. Nylund, 2007).

To date, only one previous study has applied LTA in order to examine the stability and transitions of depressive subtypes, although it is an elegant way to obtain more knowledge about this topic (Lamers, Rhebergen, et al., 2012). The study of Lamers at al. (2012) found the highest temporal stabilities for their empirically derived moderate and severe atypical subtype. In contrast, the stability coefficients for the severe typical (melancholic) subtype were slightly lower. The authors concluded that their results support the validity of these depressive subtypes. However, the study merely assessed a two-year follow-up and therefore longer time-periods are required to confirm these findings. Additionally, the factor sex was not considered as potential predictor influencing stability and transition patterns of depression subtypes.

1.8 The longitudinal Zurich Study and the cross-sectional ZInEP Epidemiology Survey

In the following two sections, a brief overview of the two surveys forming the basis for the studies of this thesis will be provided: The longitudinal Zurich Study and the cross-sectional ZInEP Epidemiology Survey.

1.8.1 The Zurich Study

The prospective, longitudinal Swiss Zurich Study (Angst et al., 1984; 2005) is based on an initial screening procedure followed by a subsequent subsample stratification. This two-phase procedure is common in epidemiological study designs (Dunn, Pickles, Tansella, & Vazquez-Barquero, 1999) and was chosen in order to enrich the sample with participants at high risk of mental disorders. In 1978, a sample of 2'201 males and 2'346 females was screened with the Symptom Checklist 90-R (Derogatis, 1977) and a socio-demographic questionnaire. Based on the global severity index (GSI) of the SCL-90-R, a stratified subsample of 591 subjects composed of two-thirds of high scorers (scoring above the 85th percentile) and one-third of randomly selected low-scorers (scoring below the 85th percentile), was comprehensively interviewed in a face-to-face setting. The Structured Psychopathological Interview and Rating of Social Consequences of Psychic Disturbances for Epidemiology (SPIKE), specially designed for the Zurich Study (Angst et al., 1984), was applied to assess the 12-month prevalence of somatic and psychopathological syndromes/disorders. The subjects were followed up over 30 years and during this period seven follow-up interviews were performed in the years 1979, 1981, 1986, 1988, 1993, 1999, and 2008.

1.8.2 The ZInEP Epidemiology Survey

The ZInEP epidemiology survey is one of nine ZInEP subprojects, which have been implemented in the intervening time. This survey was carried out under the supervision of PD Dr. phil. Vladeta Ajdacic-Gross, senior researcher at the Department of Psychiatry, Psychotherapy and Psychosomatics at the Zurich University Hospital of Psychiatry. The ZInEP survey started in 2010 and ended in 2012. With regard to the methodological design and the sex-age distribution, the survey was designed as a cross-sectional sequel to the longitudinal Zurich Study (Angst et al., 1984; Angst et

al., 2005), although a small subsample of participants was also longitudinally followed. Hence, these two surveys have the potential to be combined with the appropriate analytic strategies.

As depicted in Figure 1, the ZInEP survey is composed of three consecutive components: (a) a brief telephone screening, (b) a structured face-to-face interview completed with self-report questionnaires (focusing either on psychosis or on personality disorders), and (c) a longitudinal survey.

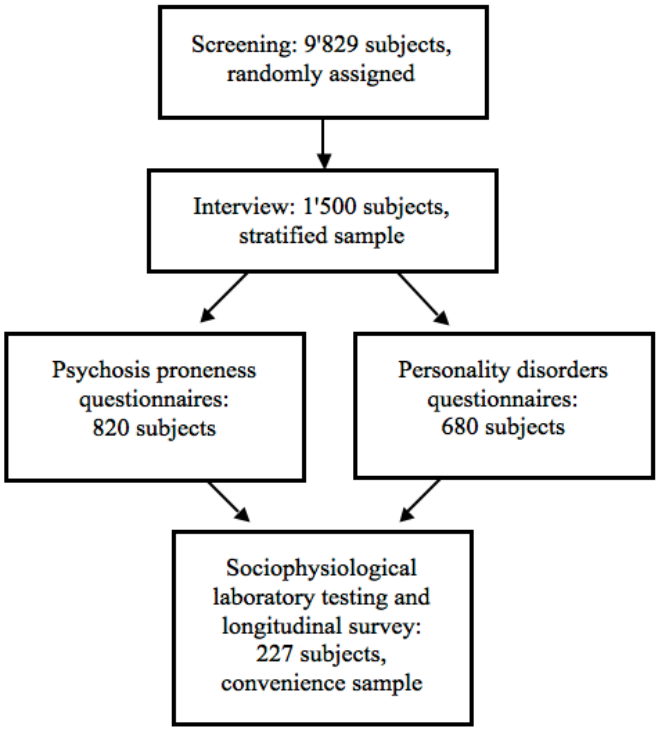

Figure 1. The sampling procedure of the ZInEP Epidemiology Survey

The initial telephone screening was performed by the GfK (Growth for Knowledge), a large market and field research institute, receiving instructions from experienced associates of the ZInEP research team. A computer assisted telephone interview (CATI) was administered using the Symptom Checklist 27 (SCL-27) (Hardt, Egle, Kappis, Hessel, & Brahler, 2004). All participants were randomly derived from the communal public authority register of the municipalities of the canton of Zurich.

A first subsample of subjects was randomly selected from the screening sample. Similarly to the Zurich Study, a sampling procedure including 60% high-scorers (scoring above the 75th percentile of the GSI of the SCL-27) and 40% low-scorers (scoring below the 75th percentile) was performed. The face-to-face interviews took place at the subjects' homes or at the Zurich University Hospital of Psychiatry and were carried out by 21 intensively trained clinical psychologists. A shortened, computer-assisted version of the SPIKE was used for the face-to-face interviews.

A second subsample was chosen for the longitudinal survey. This subsample was composed of three groups with high scores on the two psychoticism scales schizophrenia nuclear symptoms (SNS) and schizotypal signs (STS) (Rössler et al., 2007) and a control group. First, these subjects performed a set of tests during a day in the sociophysiological laboratory of the Zurich University Hospital of Psychiatry. Second, they were interviewed bimonthly over a maximum period of six month.

1.9 Research objectives

Accumulating studies yielded evidence that MDD is a highly heterogeneous construct, bearing the risk of homogenizing numerous depressive conditions with different etiopathogenetic pathways. The non-specific response of MDD to differing treatment modalities, the limited efficacy of antidepressants in only 54% of all cases, compared with 37% with placebo, and the high relapse rates of 54% within two years constitute the most important arguments for research on depression subtypes (Baumeister & Parker, 2012; Undurraga & Baldessarini, 2012; Vittengl, Clark, Dunn, & Jarrett, 2007). Person-centered methodological approaches, such as LCA and LTA have confirmed the existence of homogeneous symptom-based depression subtypes (Baumeister & Parker, 2012; Lamers, Rhebergen, et al., 2012). However, antecedent findings leave a number of important sex-related issues unresolved and there is a need for more clarity in this research area. In order to receive a more detailed insight into these issues, three studies were conducted. In the following, the main aims of each study are briefly outlined:

Study 1: The role of sex on stability and change of depression symptom subtypes over 20 years: a latent transition analysis (chapter 2, manuscript I)

Although prior studies have investigated the long-term stability of some symptom-based subtypes, none of these longitudinal depression studies considered the factor sex, despite its well-established impact on depression. Only one study has applied the promising statistical method LTA in order to analyse stability and transition of depression subtypes (Lamers, Rhebergen, et al., 2012), but this study was limited to a two-year follow-up period and omitted sex as potential predictor, as did the other previous studies.

Thus, in the first study, mixture modeling (LTA) was performed on the longitudinal Zurich Study data of subjects manifesting depressive symptoms examining the long-term stability and transition patterns (20 years) of the resultant subtypes as a function of sex. Meaningful differences between males and females were expected. In a following step, the resultant stable subtypes were characterized by psychosocial correlates.

Study 2: Symptom-based subtypes of depression and their psychosocial correlates: A person-centered approach focusing on the influence of sex (chapter 2, manuscript II)

Despite accumulating evidence demonstrating female-related symptom-based subtypes (Halbreich & Kahn, 2007), studies focusing on depressive subtypes in males are limited. Moreover, community studies using person-centered methodological approaches separately by sex are warranted.

In the second study, LCA was applied to a large, population-based sample (ZInEP study) separately by sex to derive sex-specific, sex-related and non-sex-related depressive subtypes. I aimed to replicate the depression subtypes found in manuscript I in an independent, cross-sectional sequel, parallelised regarding sex-age composition, and expected to exploratively detect further sex-specific subtypes due to the higher power resulting from the larger sample size. Additionally, I intended to investigate previously proposed concepts such as Rutz's male depressive syndrome (Rutz, 1999; Rutz et al., 1995) and gender role orientation within the framework of symptom-based depression subtypes. A male-specific subtype with a delimitable symptom profile was hypothesized, and moreover, higher scores for masculinity in non-severe depression subtypes. Finally, differing comorbidity profiles between males and females were expected.

Study 3: Serum testosterone levels and symptom-based depression subtypes in men (chapter 2, manuscript III)

Converging evidence from clinical, epidemiological and endocrinological studies has indicated that depression subtypes can be characterized by distinct biological correlates, such as dysregulations of the (HPA) stress axis (Baumeister & Parker, 2012). Whereas the examination of gonadal hormones and depression was prominently advanced in females, studies investigating gonadal hormones in males are quite rare. Nevertheless, the available studies on depressed males indicate that the associations found between low testosterone levels and overall depression may not only apply to specific subpopulations of depressives but that both low and high testosterone might be associated with increased affective symptoms. However, this evidence stems from studies examining exogenous testosterone administration on affective symptoms. To what extent endogenous testosterone levels differ between symptom-based subtypes in males has not been investigated so far.

In the third study, the testosterone concentrations in blood serum of the male depressive subgroups derived in manuscript II were examined with regard to significant differences. Based on the evidence from exogenous testosterone administration, higher/lower testosterone levels for severe depressed and hypomania/mania-associated subtypes were expected, and lower testosterone levels for moderate/mild depressed subgroups, and subgroups associated with high BMI, respectively.

Taken together, this doctoral thesis aims to extend the knowledge about sex-related differences of symptom-based depression subtypes with regard to the aspects of depressive phenomenology, course, and biopsychosocial characteristics by applying data-driven statistical mixture modeling. The data-driven approach enables the detection of new facets in an investigated issue without sticking to one, possibly restricted, theory. However, all analyses were performed with a permanent interrelation with theoretical concepts. By integrating biopsychosocial aspects and by replicating analysis in different data sets, this doctoral thesis contributes to an enhanced validity of sex-related subtypes. Valid, homogeneous subtypes may suggest distinct etiopathogenetic mechanisms, which in turn could have important implications for the development of personalized and specific depression treatments.

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2. Manuscripts

Manuscript I: The role of sex on stability and change of depression symptom subtypes over 20 years – a latent transition analysis

Stephanie Rodgers[1,*], Vladeta Ajdacic-Gross[1], Mario Müller[1], Michael P. Hengartner[1], Martin Grosse Holtforth[2], Jules Angst[1], Wulf Rössler[1,3]

[1] Zurich University Hospital of Psychiatry, Department of Psychiatry, Psychotherapy and Psychosomatics, Zurich, Switzerland

[2] Department of Psychology, University of Zurich, Switzerland

[3] Collegium Helveticum, a Joint Research Institute between the University of Zurich and the Swiss Federal Institute of Technology, Zurich, Switzerland

* Corresponding author

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Abstract

Prospective studies investigating the long-term stability of depression symptom subtypes are rare. Moreover, sex has received little attention as a predictor. This study aimed to investigate the role of sex on stability and transition patterns of depressive symptom subtypes over 20 years.

The data were drawn from three follow-ups (1988, 1999, and 2008) of the longitudinal Zurich Study. Latent transition analyses were fitted to the data of 322 subjects, using depressive symptoms from the face-to-face interviews. The stable classes were characterized by psychosocial correlates.

Three subtypes were identified: 'severe atypical', 'severe typical', and 'moderate'. While stability of the severe atypical and moderate subtype was relatively high and increased over time (70-71; 45-90%), stability of the severe typical subtype was lower (45-48%). Females had a higher risk of being in the severe atypical subtype and exhibited more transitions, particularly with respect to the severe typical subtype. In contrast, males displayed more stable subtypes. The stable severe atypical subtype was associated with comorbid eating disorders as well as psychosis syndromes, whereas the stable severe typical subtype was associated only with psychosis syndromes.

Our results provide first evidence for the notion that long-term stability and transition patterns differ by sex and depression subtypes. This finding has received too little attention in previous research and should be considered in treatments.

Key words:
Depression; Subtypes; Sex; Longitudinal studies; Epidemiology

Introduction

Over the past decades the recognition of the heterogeneity of major depressive disorder (MDD) resulted in the development of various depression subtype models. Research on subtypes of MDD is a promising approach towards a better understanding of etiology and type-specific treatments [10]. Three symptom-based subtypes are currently coded in the diagnostic and statistical manual of mental disorders (DSM-5) as the MDD specifiers: melancholic, atypical and psychotic depression [9]. In addition to the diagnostic classification system, there is a growing body of evidence from empirically derived symptom typologies based on cluster analysis and latent class analysis (LCA), confirming the existence of MDD subtypes [12, 18, 24, 28, 29, 42, 54, 55]. However, only few studies have investigated the longitudinal stability of MDD symptom subtypes, although the temporal stability displays an important aspect of the usefulness of subtype classifications [23]. Subsequently, these longitudinal findings of the melancholic, atypical, and psychotic subtype will be summarized:

Firstly, studies investigating the stability of the melancholic subtype have yielded rather inconsistent findings. This may be attributable to the various definitions of melancholia and similar concepts such as endogenous depression and typical depression [10, 34]. Some studies found stability values between 30% (community-based sample) [4] and 37% (depressed inpatients) [23]. Other studies demonstrated a weak stability of the melancholic subtype in depressed in- and outpatients, leading to concerns regarding the validity of this MDD specifier [34, 60].

Secondly, the atypical depression demonstrated a moderate stability in the community-based longitudinal Zurich Study [7]. A further study showed that 90% of depressive outpatients with reversed symptoms (hypersomnia, overeating, weight gain) at baseline manifested the same symptoms when they relapsed [38]. This stability was consistent with genetic epidemiology data of female twins, suggesting a genetic stability of the atypical subtype [24]. Yet in a small sample of atypical depressive patients, one-third with first onset of affective disorder was no longer atypical within a two-year follow-up [19, 27].

Thirdly, the stability of the psychotic subtype was confirmed by the finding that 92-95% of psychotic depressive patients experienced another admission for an episode of depression with psychotic syndromes [13, 22]. Comparing the psychotic, agitated/retarded, and endogenous subtypes of

depression, the psychotic subtype showed the highest diagnostic stability across multiple episodes. However, some authors [33] proposed that major depression with mood-congruent psychotic symptoms may not be a distinct diagnostic entity, but rather a more severe occurrence of depression.

However, complementary to stability issues, some research has provided support for the view that a shift from one depressive subtype to another might be common [4, 32]. Therefore, apart from the validation of depression-subtype stability, the investigation of transitions between the depression subtypes should be clarified in more detail. For examining the transitions between depression subtypes, the application of more suitable statistical methods is warranted than have been used in previous research.

A promising statistical approach for extracting homogenous subgroups is LCA. The latent transition analysis (LTA) is the longitudinal extension of LCA, allowing for the estimation of stability and transition patterns among subtypes. To date, only one study has applied LTA to examine the transitions and stability of MDD subtypes longitudinally over a two-year follow-up period [30]. The highest stability over time was found for the moderate and the severe atypical classes. The probabilities for the severe typical class were slightly lower. The findings indicated relative stability across measurements and thereby confirmed the validity of these depressive subtypes. As Lamers et al. [30] noted, future research should investigate whether these patterns of stability and transitions are still identifiable over longer time periods.

In this context, previous longitudinal research has not taken sex into consideration as a potential predictor, despite the consistent empirical findings of higher rates of MDD in females [25, 57]. However, these findings have been explained by specific symptom-based depressive subtypes in females such as atypical, anxious, and somatic depression [7, 11, 15, 51, 52]. The inconsistent empirical evidence regarding sex differences in the course of MDD [47] could derive from the fact that MDD is a highly heterogeneous construct that should more appropriately be analyzed within the scope of symptom subtypes, their longitudinal stability as well as transition patterns.

Aims of the study

Therefore, the aims of the current study were: (1) to investigate the long-term stability and transitions of symptom-based depression subtypes over a period of 20 years, (2) to examine whether stability and transition patterns of these symptom subtypes meaningfully differ between males and females, and (3) to characterize resulting stable subtypes by relevant psychosocial correlates.

Methods

Study design and sample selection

The data were drawn from the prospective longitudinal Zurich Study [6]. The Zurich Study is based on an initial screening procedure. In 1978, a representative sample of young adults of the canton of Zurich in Switzerland was screened with the Symptom Checklist 90-R (SCL-90-R; [16]), and a socio-demographic questionnaire. This sample comprised 4,547 subjects (males=2,201; females=2,346), aged 19 years (males) and 20 years (females). Subsequently, a stratified sampling procedure was performed. This methodological approach was utilized to increase the proportion of subjects with a high risk of developing psychiatric syndromes/disorders in the sample. Based on the global severity index (GSI) of the SCL-90-R, two-thirds of high scorers (above the 85th percentile) and one-third of randomly assigned low scorers (below the 85th percentile) were selected, leading to a final subsample of 591 subjects (292 males; 299 females). Over 30 years, seven follow-up interviews were conducted in 1979, 1981, 1986, 1988, 1993, 1999, and 2008. The study was approved by the local ethics committee.

Of the original sample (*n*=591), 335 (57%) participated in the last follow-up 2008. The detailed participation rates were as follows: 43% in all seven interviews, 13% in six interviews, 11% in five interviews, 9% in four interviews, 7% in three interviews, 9% in two interviews, and 9% in one interview.

For the current study, the data of subjects who participated in any of the interviews 1988, 1999, and 2008 were included in the analyses. The restriction to these three follow-ups was made to keep the indicators identically over time and because the previous assessments differed with respect to the assessed depression symptoms. The follow-up 1993 was omitted in order to receive nearly equidistant time intervals.

The data of participants with missing data on all three follow-ups 1988, 1999, and 2008 were excluded from the analyses (*n*=269). This led to a final subsample of 322 participants. The data of those subjects giving information at only one or two occasions, respectively, were considered in the LTA. In this context, the following patterns of missing data were observed: missing data on all items in *one* follow-up: 1988 *n*=44 (13.7%); 1999 *n*=23 (7.1%); 2008 *n*=37 (11.5%); and missing data on all items on *two* follow-ups: 1988 and 1999 *n*=31 (9.6%); 1999 and 2008 *n*=84 (26.1%); 1988 and 2008 *n*=55 (17.1%). According to Little's MCAR test (χ^2=452.751, *df*=438, *p*=0.303), these missing values were missing completely at random (MCAR). We decided not to impute the data of complete follow-ups to maintain the data quality as high as possible and to improve the estimation of the time-specific parameters. However, 17 participants (5.3%) had missing values on one item and in one case on two items in 1999, despite they participated in the interview. The Little's MCAR test (χ^2=56.085, *df*=59, *p*=0.584) revealed again that these missing values were MCAR. Based on the subjects' complete items of 1999, the missing values were replaced by values derived by multiple imputation, which relies on Bayesian analysis [45, 46] in Mplus.

After performing the LTA, we selected subjects remaining in the same class over the three time points 1988, 1999, and 2008 in order to characterize these resulting stable subtypes. This led to a subsample of 174 subjects.

Measures

The Structured Psychopathological Interview and Rating of Social Consequences of Psychic Disturbances for Epidemiology (SPIKE) is a comprehensive face-to-face interview assessing a number of somatic and psychopathological syndromes/disorders for the previous 12 months [3]. The SPIKE was administered in the participants' homes by clinical psychologists or psychiatrists trained intensively in the use of the instrument [2]. Validity and reliability have been established particularly for depression and anxiety. The inter-rater reliability of the SPIKE was high, with kappas of 0.90 for

the syndromal diagnosis. Moreover, the SPIKE was found to have high sensitivity and modest specificity for detecting depression at the diagnostic level and a good sensitivity with respect to the subthreshold level [6].

For the current study, algorithms of psychiatric diagnoses were used according to the respective version of DSM-III, DSM-III-R, DSM-IV, and ICD-10 [6, 8, 58]. Furthermore, the presence of the two psychosis syndromes psychoticism and paranoia was computed using the schizophrenia nuclear symptoms (SNS) and schizotypal signs (STS) subscales [44] derived from the SCL-90-R [17].

Only subjects affirming either the first or second filter question of the section depression were included in the data analyses. We considered 15 binary-coded depressive symptoms ('Symptom existent during the past 12 month?' 0=no; 1=yes) representing the nine DSM-IV 'A' criteria for major depression. Additionally, we disaggregated appetite loss/gain, weight loss/gain, insomnia/hypersomnia, and psychomotor agitation/retardation, due to the fact that these criteria are antipodal, and moreover, we included the atypical feature 'irritability/anger'. These symptoms were assessed for the time frame of the last 12 month without considering criteria of frequency and durability.

Statistical analysis

Latent transition analysis (LTA) is a longitudinal mixture model that accounts for individual transitions between categorical latent classes over time [37, 39]. Based on the interindividual response pattern to manifest items, homogeneous subgroups (latent classes) of individuals are extracted. At each time of measurement, an LCA is postulated, and stage-sequential development is summarized in transition probability of latent classes over two serial times. When covariates are considered, transition probabilities are conditioned not only by the previous time point, but also as a function of the value of the covariate [39]. The resultant measurement parameters are the transition probabilities from time 1 to 2, time 2 to 3, etc., the class membership probability, and the conditional item probabilities, estimated for each class at the several time points [14, 39].

Commonly used statistical fit indices for model comparisons are the Bayesian information criterion [BIC; 49], the sample-size adjusted BIC [ABIC; 50], and the entropy measure (ranging from 0 to 1). Low BIC and ABIC values and a high entropy index indicate a better model fit. The final selection is

commonly guided by the combination of the statistical fit indices with the theoretical interpretability of a given class solution [35].

First, exploratory cross-sectional LCA was performed for the years 1988, 1999 and 2008. To determine the optimal number of latent classes, one to five latent class models were fitted to the data. These models were compared by BIC, ABIC, and entropy. After performing the unconditional LCA, the covariate sex was included at each time point. Second, we explored whether full (all conditional item probabilities are equal) or partial (part of the conditional item probabilities are equal) measurement invariance should be assumed across the time points [39]. This was performed using deviance statistic [53]. Given that the chi-square value of partial invariance and full noninvariance was not significant, partial measurement invariance was assumed for the time points 1988, 1999, and 2008. Finally, longitudinal LTA was fitted to the data for the three time-points 1988 to 1999 to 2008 (age: 29-50). Latent transition probabilities were first computed in a unconditional model without a covariate and subsequently in a conditional model including the covariate sex (providing an output separately for each covariate group).

Latent class analysis (LCA), LTA, and multiple imputation were carried out using Mplus, version 7, for Macintosh [37]. In each analysis, the number of random starts was set up to 5,000, using the 500 best solutions in the final calculation. Chi-square tests, Fisher's exact tests, Kruskal-Wallis tests, and multinomial logistic regressions (odds ratios [OR] with 95% confidence intervals [CI]) were computed using SPSS statistics, version 20, for Macintosh (SPSS Inc., USA).

Results

Model selection on the basis of latent class analysis

Five exploratory LCA models were fitted to each of the three time-points 1988 (*n*=192), 1999 (*n*=184), and 2008 (*n*=146). Table 1 compares the resulting model fit indices, beginning with the most parsimonious one-class model through to a five-class model. The BIC and ABIC indicated that the three- or four-class solution provides the best fit to the data. After a comparison of the plotted

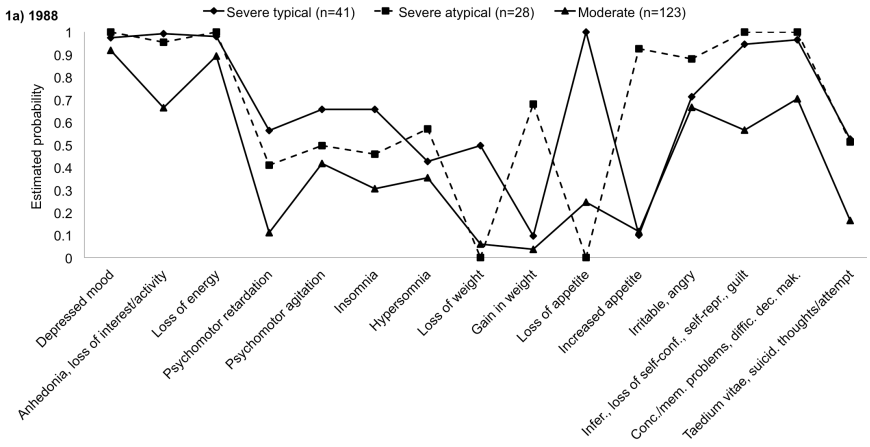
estimated symptom probabilities, the three-class LCA model was chosen, as more classes produced only further moderate classes of questionable meaning.

Table 1. Model fit indices derived from latent class analysis with classing ranging from 1 to 5 of the subsamples of subjects with depressive symptoms: 1988, 1999, and 2008

Fit statistics	1-class	2-class	3-class	4-class	5-class
1988					
BIC	3,129.496	3,072.124	3,071.092	3,077.914	3,130.418
ABIC	3,081.981	2,973.925	2,922.210	2,878.350	2,880.171
Entropy	N/A	0.674	0.781	0.865	0.896
1999					
BIC	2,982.627	2,952.934	2,946.428	2,978.587	3,026.775
ABIC	2,935.118	2,854.749	2,797.567	2,779.050	2,776.563
Entropy	N/A	0.686	0.794	0.855	0.934
2008					
BIC	2,384.924	2,331.032	2,372.208	2,420.004	2,470.751
ABIC	2,337.457	2,232.935	2,223.479	2,220.644	2,220.759
Entropy	N/A	0.748	0.842	0.857	0.882

BIC Bayesian information criterion, *ABIC* sample-size adjusted Bayesian information criterion (ABIC).

The plotted estimated symptom probabilities showed that class one was characterized by a high probability for typical depressive symptoms such as loss of weight and appetite. Therefore, this class was labeled ‘severe typical’. Subjects of class two endorsed symptoms such as weight gain and increased appetite. Because of its high probabilities for an atypical symptom pattern, this class was labeled ‘severe atypical’. Finally, the third class exhibited less pronounced symptom probabilities and was labeled ‘moderate’. The inclusion of the covariate sex at each time point indicated significant sex differences with respect to the latent classes with a higher proportion of females in the severe atypical class. Figure 1 depicts the plots of the estimated symptom probabilities derived from the LCA after inclusion of the covariate sex for each time point.



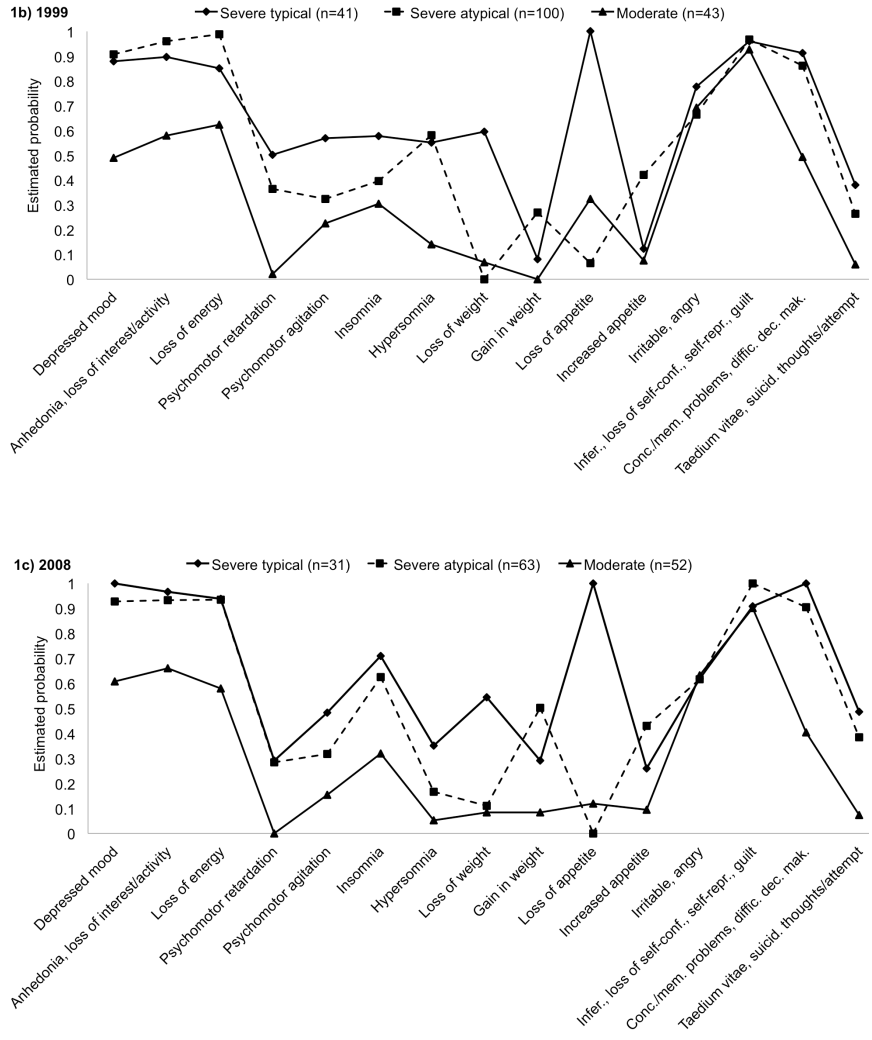


Fig. 1. Symptom probability plots across the three latent classes with the covariate sex at

a) 1988. Aggregated items: feelings of inferiority, loss of self-confidence, self-reproaches, excessive guilt, concentration/memory problems, difficulties in decision making; disaggregated items: appetite loss/gain, weight loss/gain, insomnia/hypersomnia; psychomotor agitation/retardation
b) 1999. Aggregated items: anhedonia, loss of interest and activity, feelings of inferiority, loss of self-confidence, self-reproaches, excessive guilt, concentration/memory problems, difficulties in decision making, tiredness of life (taedium vitae), suicidal ideation, suicidal attempt; disaggregated items: appetite loss/gain, weight loss/gain, insomnia/hypersomnia; psychomotor agitation/retardation
c) 2008. Aggregated items: anhedonia, loss of interest and activity, feelings of inferiority, loss of self-confidence, self-reproaches, excessive guilt, concentration/memory problems, difficulties in decision making, tiredness of life (taedium vitae), suicidal ideation, suicidal attempt; disaggregated items: appetite loss/gain, weight loss/gain, insomnia/hypersomnia, psychomotor agitation/retardation.

Latent transition analysis

The estimated transition and stability probabilities derived from the LTA are presented in Table 2. Compared to the unconditional model, the stability coefficients of the conditional model including the covariate sex were quite similar. In the conditional model, class stability was higher in the moderate and severe atypical class than in the severe typical class. Remarkably, the stability of the moderate class even increased in the second time period above 90%, while the severe typical and severe atypical class nearly remained unchanged.

When individuals transitioned to a different class over time, they predominantly changed from the severe typical to the severe atypical and moderate classes. However, noteworthy transitions also occurred from the severe atypical to the severe typical class, whereas moves from the moderate to the severe atypical class declined over time.

Sex ratios were computed for the LTA classes of the conditional model (not tabulated). In 1988, multinomial logistic regressions revealed a significantly higher risk for females belonging in the severe atypical latent class (OR 2.84, CI 1.18–6.83) (typical class: *n*=33 males, *n*=22 females; atypical class: *n*=7 males, *n*=25 females; moderate class: *n*=105 males, *n*=132 females). In 1999, the odds ratio associated with the severe atypical class (OR 2.35, CI 1.43–3.88) was significantly higher for females (typical class: *n*=31 males, *n*=21 females; atypical class: *n*=39 males, *n*=88 females; moderate class: *n*=73 males, *n*=70 females). In 2008, there was still a significantly higher risk for females being in the severe atypical class (OR 1.81, CI 1.10–2.96) (typical class: *n*=27 males, *n*=22 females; atypical class: *n*=41 males, *n*=78 females; moderate class: *n*=75 males, *n*=79 females).

The latent transition probabilities of the conditional model revealed meaningful sex differences (Table 2). Males exhibited a higher stability within the latent classes, and moreover, stability substantially increased over time. Interestingly, transitions were more prominent in females for both time intervals, particularly regarding movements from the severe typical to the severe atypical class and vice versa. In contrast, no male transitioned from the atypical class to the typical class. In addition, females revealed changes from the severe typical class into the moderate class.

Table 2. Estimated transition and stability (bold) probabilities across the time points 1988 to 1999 to 2008 for the unconditional model, the conditional model including the covariate sex and separately for males and females, *n*=322

	Unconditional model (overall)			**Conditional model (overall)**			**Conditional model (males)**			**Conditional model (females)**		
	1999			***1999***			***1999***			***1999***		
1988	Severe typical	Severe atypical	Mod-erate	Severe typical	Severe atypical	Mod-erate	Severe typical	Severe atypical	Mod-erate	Severe typical	Severe atypical	Mod-erate
Severe typical	**0.370**	0.443	0.187	**0.446**	0.354	0.200	**0.543**	0.122	0.334	**0.359**	0.562	0.079
Severe atypical	0.332	**0.607**	0.061	0.149	**0.704**	0.148	0.000	**0.545**	0.455	0.192	**0.750**	0.059
Mod-erate	0.093	0.412	**0.495**	0.123	0.426	**0.451**	0.089	0.483	**0.428**	0.157	0.370	**0.473**
1999	***2008***			***2008***			***2008***			***2008***		
Severe typical	**0.367**	0.409	0.224	**0.481**	0.292	0.227	**0.666**	0.334	0.000	**0.344**	0.261	0.395
Severe atypical	0.238	**0.672**	0.089	0.198	**0.708**	0.094	0.000	**0.765**	0.235	0.324	**0.671**	0.005
Mod-erate	0.000	0.117	**0.883**	0.024	0.074	**0.902**	0.046	0.000	**0.954**	0.000	0.157	**0.843**

Psychosocial correlates of stable depression subtypes

Longitudinally stable subtypes might be more reliable than subtypes derived cross-sectionally [30]. Consequently, for the next analysis, we selected persons exhibiting the same class membership over the three time points 1988, 1999, and 2008 and excluded subjects transitioning between the three subtypes at least once. This led to a subsample of 174 persons [severe atypical class: *n*=19 (10.9%); severe typical class: *n*=26 (14.9%); moderate class: *n*=129 (74.1%)]. In terms of demographics, the latent stable classes differed significantly by sex. The severe atypical subtype comprised significantly more females, whereas the severe typical subtype included significantly more males. The sex proportion of the moderate class was almost in balance. Further psychosocial characteristics of the stable subgroups are presented in Table 3.

Table 3. Psychosocial characteristics for the stable classes (*n*=174) derived from latent transition analysis including the covariate sex

	Latent Classes			
	Severe typical ***n*****=26** **% (*n*)**	**Severe atypical** ***n*****=19** **% (*n*)**	**Moderate** ***n*****=129** **% (*n*)**	**χ^2/F-Test Overall *p* value (two-tailed)**
Sex				$p<0.001^{I, II, III}$
Female	11.5 (3)	94.7 (18)	50.4 (65)	
Male	88.5 (23)	5.3 (1)	49.6 (64)	
Education [1]				$p=0.437$
Secondary general school	43.5 (10)	27.8 (5)	35.8 (44)	
Intermediate secondary school	43.5 (10)	33.3 (6)	35.8 (44)	
Grammar school	13.0 (3)	38.9 (7)	28.5 (35)	
Familiar depression [2]	26.9 (7)	16.7 (3)	13.6 (17)	$p=0.228$
Comorbid psychiatric disorder/syndrome (lifetime)				
MDD [b]	26.9 (7)	15.8 (3)	17.8 (23)	$p=0.500$
MDD/DYST/ RBD/MIND [b]	92.3 (24)	84.2 (16)	71.3 (92)	$p<0.05^{III}$
MDD and manic symptoms [c]	38.5 (10)	47.4 (9)	21.7 (28)	$p<0.05^{II}$
Neurasthenia [d]	23.1 (6)	31.6 (6)	14.7 (19)	$p=0.140$
GAD [a]	42.3 (11)	57.9 (11)	21.7 (28)	$p<0.01^{II, III}$
Simple Phobia [b]	15.4 (4)	26.3 (5)	14.0 (18)	$p=0.321$
Agoraphobia [b]	15.4 (4)	31.6 (6)	8.5 (11)	$p<0.05^{II}$
Social phobia [b]	26.9 (7)	42.1 (8)	15.5 (20)	$p<0.05^{II}$
OCD [b]	11.5 (3)	10.5 (2)	5.4 (7)	$p=0.311$
Panic disorder [a]	15.4 (4)	10.5 (2)	8.5 (11)	$p=0.480$
Psychoticism syndrome [e]	31.6 (6)	16.7 (3)	1.1 (1)	$p<0.001^{II, III}$
Paranoia syndrome [e]	26.3 (5)	38.9 (7)	6.5 (6)	$p<0.001^{II, III}$
Bulimia [b,c]	3.8 (1)	15.8 (3)	1.6 (2)	$p<0.05^{I, II}$
Binge eating (at least symptoms) [b,c]	8.0 (2)	37.5 (6)	9.4 (12)	$p<0.01^{I, II}$
Tobacco dependence [a]	73.1 (19)	47.4 (9)	52.7 (68)	$p=0.129$
Alcohol abuse/dependence [c]	46.2 (12)	52.6 (10)	30.2 (39)	$p=0.072$
Substance abuse/dependence [c]	30.8 (8)	10.5 (2)	15.5 (20)	$p=0.151$
	Mean rank (*n*)	**Mean rank (*n*)**	**Mean rank (*n*)**	**Kruskal-Wallis test *p* value**
Childhood/adolescence adversity [3]				
Family/conduct problems (total score)	78.0 (24)	98.5 (19)	70.1 (106)	$p<0.05$
Critical life events [4]				
New job	70.2 (26)	97.1 (19)	88.3 (127)	$p=0.130$
Unemployment	80.6 (26)	85.7 (19)	87.8 (127)	$p=0.753$
To move house	72.0 (26)	85.5 (19)	89.6 (127)	$p=0.223$
Financial difficulties	72.4 (25)	76.7 (19)	80.8 (113)	$p=0.170$

MDD major depression disorder, DYST dysthymia, RBD recurrent brief depression, MIND minor depression, GAD generalized anxiety disorder, OCD obsessive-compulsive disorder

[1] *n*=10 missing data

[2] Mother, father, brother/sister, including several family members *n*=5 missing data

[3] Derived from tetrachoric factor analysis; *n*=25 missing data

[4] Sum of critical life events (1988, 1999, 2008); *n*=1-17 missing data

[a] DSM-III; [b] DSM-III-R; [c] DSM-IV; [d] ICD-10; [e] schizophrenia nuclear symptoms (SNS) and schizotypal signs (STS) subscales (Rössler et al. [44])

[I] Class 1 significantly differs from class 2; [II] Class 1 significantly differs from class 3; [III] Class 2 significantly differs from class 3.

Table 4 displays odds ratios and confidence intervals (95%) from multinomial logistic regressions, characterizing the comorbidity patterns of stable classes. The moderate class is treated as reference class. Bulimia/binge eating and psychosis syndromes were significantly associated with an increased risk of membership in the severe atypical class in comparison with the moderate class. On the other hand, the severe typical class differed from the moderate class solely with respect to psychosis

syndromes. Additional multinomial logistic regression analyses contrasting the severe typical subtype versus the severe atypical subtype showed a significantly (p<0.01) lower risk of bulimia/binge eating (OR 0.08, CI 0.01–0.46) in the severe typical class (not tabulated). While childhood/adolescence adversity was linked to the severe atypical class, unemployment was a critical life event characterizing the severe typical class.

Table 4. Odds ratios and confidence intervals (95%) from multivariate multinomial logistic regressions for the stable classes (n=174) derived from latent transition analysis including the covariate sex (severe atypical class: n=1 male, n=18 females; severe typical class: n=23 males, n=3 females; moderate class: n=64 males, n=65 females)

	Latent Classes	
	Severe atypical vs. moderate (ref.)	**Severe typical vs. moderate (ref.)**
Education		
Secondary general school	0.54 (0.10–2.99)	2.63 (0.45–15.24)
Intermediate secondary school	0.42 (0.07–2.35)	2.44 (0.45–13.14)
Grammar school (referent)		
Familiar depression	1.44 (0.20–10.25)	0.30 (0.06–1.42)
Comorbid psychiatric disorder/syndrome (lifetime)		
Any affective disorder	0.82 (0.10–7.05)	1.45 (0.22–9.44)
Any anxiety disorder	1.17 (0.28–4.88)	2.22 (0.58–8.48)
Alcohol/drug disorder	1.41 (0.30–6.54)	1.08 (0.26–4.43)
Bulimia/binge eating	13.00 (2.40–70.53)**	1.22 (0.12–12.76)
Psychosis syndromes	13.78 (2.31–82.31)**	7.38 (1.64–33.23)**
Childhood/adolescence adversity		
Family/conduct problems (total score)	1.32 (1.03–1.70)*	0.93 (0.73–1.19)
Critical life events		
New job	2.78 (0.80–9.60)	0.41 (0.16–1.06)
Unemployment	0.52 (0.09–3.14)	4.01 (1.07–14.95)*
To move house	0.41 (0.10–1.73)	0.36 (0.13–1.04)
Financial difficulties	1.26 (0.09–18.60)	0.26 (0.04–1.92)

Affective disorders: MDD, dysthymia, recurrent brief depression, minor depression, MDD with manic symptoms, neurasthenia; anxiety disorders: agoraphobia, obsessive-compulsive disorder, simple phobia, panic disorder, generalized anxiety disorder, social phobia; alcohol/drug disorders: alcohol abuse/dependence, substance abuse/dependence, tobacco dependence; psychosis syndromes: psychoticism, paranoia
For detailed information with respect to the used variables, see Table 3
Ref reference
*p<0.05, **p<0.01, ***p<0.001.

Discussion

This study aimed at analyzing the role of sex on stability and transition patterns of empirically derived depression subtypes in a prospective epidemiologic sample over 20 years. To the best of our knowledge, this is the first latent transition analysis study examining such a long time period. We identified three depression subtypes – ‘severe atypical’, ‘severe typical’, and ‘moderate’ – with relevant sex-related differences in the long-term stability and the transition patterns. Between 29 and 50 years of age, stability of depression subtypes strongly increased in males. In contrast,

females displayed more transitions between the subtypes. The subtype with the highest instability and the most transitions was the severe typical subtype, and especially, changes to the severe atypical subtype and vice versa were prominent.

Latent transition analysis: from cross-sectional to longitudinal evidence

The empirical identification of the subtypes 'severe atypical' and 'severe typical' is in line with the MDD specifiers of DSM-IV and with the results of earlier subtyping studies [24, 29, 30, 54, 55]. The fact that we could distinguish a moderate subtype from the two severe subtypes is also consistent with previous reports, suggesting that both symptom patterns and severity meaningfully contribute to explaining the heterogeneity of MDD [28]. However, our analyses were longitudinal and therefore provide evidence regarding the long-term validity of these psychopathological constructs. In the following, we will focus on longitudinal studies investigating depression subtypes.

In line with previous findings of atypical depression being characterized by longer episodes and higher chronicity than other subtypes [7], the current study found a high stability of the severe atypical subtype over time. The only previous study applying LTA to symptom-based depression subtypes was conducted by Lamers et al. [30]. They found similar stability values for the atypical subtype (79%) and moderate subtype (78%), but obtained much higher stability coefficients for the severe typical subtype (71%). However, consistent with the present study, two previous studies found stability coefficients for the melancholic (typical) subtype of 37% [23] and 30% [4], respectively. One of the two studies, conducted by Angst et al. [4], and the current study were based on the same sample, but differed with regard to procedures and methodology. Angst et al. computed subtypes for all six interviews, while we restricted the number of follow-ups to three interviews. Methodologically, our subtypes were estimated by a data-derived technique, while Angst and colleagues defined the subtypes by DSM-IV specifiers. More precisely, our methodological approach was person-centered (focus on relationships between individuals; goal: to group individuals into homogeneous categories); by contrast, Angst et al. had a variable-centered approach (focus on relationships between variables; goal: to predict outcomes) [36]. In contrast to our three derived subtypes, Angst et al.'s study additionally investigated a combined group manifesting melancholia or atypical depression and a subgroup with an unspecified syndrome.

The transition patterns we found in our study were similar to those earlier observed by Lamers et al. [30]. The membership changes occurred from the moderate to the severe atypical, from the severe atypical to the severe typical, and from the severe typical to the moderate subtypes. Minor discrepancies in our findings (moves from the severe typical to the severe atypical subtype) might be explained by dissimilar time frames and further methodological differences in Lamers et al.'s [30] study such as sample characteristics (no pure community sample), a broader age range (18-65 years), differing eligibility criteria (MDD diagnosis at both baseline and follow-up), and the exclusion of certain primary clinical diagnoses, such as psychotic disorder, bipolar disorder and addiction disorder.

Sex-related differences: a) instability of depression subtypes in females

As mentioned above, our results generally indicated that females' phenotype of depression longitudinally exhibited a heterogeneous presentation, with syndromes changing more frequently and a lower stability within distinct symptomatic subtypes of depression. Notably, our results indicated that the questionable validity of the typical subtype [34] concerned especially females. On the basis of our results, we speculate that the more frequent transitions across the three depressive subtypes in women may be explained by hormonal fluctuations of the perimenstrual phase. In support of this notion, results of prospective epidemiologic surveys have revealed a clear cycle-dependent vulnerability for affective symptoms [26, 43].

In our analyses, the transitions from the severe typical to the atypical class and vice versa were particularly pronounced. Recently, a biological link between changing profiles of typical (melancholic) and atypical subtypes has been proposed as a 'switch hypothesis', considering specific regulations of the hypothalamic-pituitary-adrenal (HPA) axis [40], which, in turn, is influenced by ovarian hormones [59]. Consideration of bipolar disorders I/II might provide further explanation for instability of depressive syndromes in females. Although there are no sex differences in lifetime prevalence of bipolar disorders, the phenomenology differs with respect to a higher number of depressive episodes and of rapid-cycling patterns in bipolar females, as opposed to more manic episodes in bipolar males [26, 31, 56].

Sex-related differences: b) sex-related stable depression subtypes

The stable severe atypical, severe typical, and moderate subtypes demonstrated considerable sex differences. As expected, the stable severe atypical subtype was significantly related to female sex compared to both the moderate and the severe typical subtypes. These results are in line with the finding that the sex ratio consistently found in depression might be attributed to atypical features [7, 11, 20]. On the contrary, the stable severe typical subtype showed a higher proportion of males. Our findings are in accordance with a previous analysis of Zurich Study data, in which the typical subtype (melancholia) occurred somewhat more frequently among males [4].

Sex-related differences: c) stability of depression subtypes in males

In males, the long-term stability of depression subtypes was more pronounced in comparison with females. Whereas the overall prevalence of MDD is higher for females [25, 57], for the group of males manifesting stable severe subtypes the course is chronic, at least over the examined time span of 20 years. Considering the generally higher suicide rates of males [21], the group of males of the stable severe subtypes deserves particular attention in research and practice.

Psychosocial correlates of stable depression subtypes

Above and beyond the sex-related differences, the stable depression subtypes differed with respect to comorbid disorders, childhood/adolescence adversity, and critical life events. While childhood/adolescence adversity was more pronounced in the severe atypical subtype, unemployment was significantly associated with the severe typical class. However, as Baumeister and Parker [10] noted in there recent meta-review, previous psychosocial correlates, which have been proposed to characterize melancholic (typical) depression, revealed inconclusive results. For atypical depression, they were restricted to rejection sensitivity [10]. The stable severe subtypes differed from the moderate subtype with respect to the following comorbid lifetime disorders: (1) The severe atypical subtype was characterized by a significantly higher risk of bulimia/binge eating and psychosis syndromes. The association between eating patterns and atypical depression in females [7] has been explained by a common heredity [for an overview see 20]. (2) The severe typical subtype only showed a higher risk of comorbid psychosis syndromes. Thus, in our data, the occurrence of psychosis was a matter of severity.

Moreover, there is an ongoing debate in psychopathology research whether depression is best modeled using a unitarian or a binary model [41]. In the present study, the two stable severe subtypes seem to present symptom clusters, suggesting an underlying continuum, concordant with the unitarian concept of psychiatric disorders proposing a continuum from affective to schizophrenic syndromes [for an overview see 1]. This assumption is in accordance with our classificatory analyses, as Parkers [41] claims a paradigm shift in classifying depressive disorders considering both dimensional and categorical models ('mix and match' modeling paradigm). Hence, in contrast to the current DSM-IV specifiers, we did not detect the psychotic subtype as a distinct subgroup. This supports the view that psychotic depression is rather a more severe subtype of depression [33].

The comparison of the stable severe atypical with the severe typical subtype showed significant differences regarding the comorbid disorder bulimia/binge eating. The associations of atypical depression with comorbid panic disorder, social phobia, generalized anxiety disorder, obsessive-compulsive disorder, and bipolar II disorders found in previous research [5, 7, 11] could not be replicated here multivariately. How can the discrepant co-occurrence of comorbid disorders found in previous studies and in our study be explained? Levitan et al. [32] identified a group of depressed subjects fluctuating between typical and atypical episodes, which manifested high rates of comorbid disorders. The authors believe that the inclusion of this subgroup in the investigation of atypical depressed has led to an overestimation of comorbid disorders in previous research [32]. Consequently, we can support the view of Levitan et al. [32]. The differentiation between the stable atypical and typical subtype seems to be restricted, if at all, to eating syndromes such as bulimia [32]/binge eating.

Taken together, we found more similarities than discrepancies between the two severe depression subtypes regarding the profile of comorbid disorders. This finding has also been reported by Angst et al. [4]. In the current analyses, however, the strongest delineations between the severe atypical and severe typical subtypes emerged from the symptom profiles and the factor sex.

Limitations and strengths

The following limitations of our study need to be acknowledged. First, the data contained some missing values regarding complete follow-ups. Yet, when we replicated the analyses in an exploratory approach with multiple imputation, the main results did not change. Second, the single

mental syndromes/disorders were aggregated into broad categories in the multivariate logistic regression analyses due to the small cell sizes and in order to gain a tightly structured overview of the comorbidity profiles of the stable latent classes. Therefore, the variance of these single disorders, such as GAD, was attenuated. Third, the data did not contain any information about diagnosed personality disorders, although they were associated with atypical depression [48]. It has been suggested that this association could be particularly high for individuals who oscillate between typical and atypical features [32]. Fourth, we restricted the LTA indicators to the section depression for statistical reasons of parsimony, although somatic and anxious depression phenotypes have also been considered as female specific [15, 52]. Fifth, it could be argued that we should have limited our analyses to subjects meeting the criteria of an MDD. We intentionally remained on the depressive symptom level in order to account for the significance of subthreshold symptomatology, as already done in a recent latent analysis approach [12]. Furthermore, we did not exclude subjects with bipolar disorders or psychosis to allow for the investigation of the whole spectrum ranging from affective syndromes to psychosis syndromes. Sixth, we focused on symptom-based depressive subtypes and omitted other depressive subtyping models such as time of onset-based subtypes containing early- and late-onset depression and seasonal affective disorder [10]. Seventh, we cannot exclude the possibility that the observed changes in disorder characteristics are the result of differing raters.

Notwithstanding these limitations, this is the first study utilizing latent transition models to investigate the role of sex on stability and transition patterns over a time period of 20 years. The positive news for the persons providing data is that we could observe some transitions from severe subtypes into the moderate group, which is hopefully associated with a decreasing disease burden. On the other hand, the considerable longitudinal stability of atypical depression strongly suggests the provision of type-specific treatments [10]. The development of such type-specific treatments will be of particular importance to adequately address sex-specific requirements.

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Manuscript II: Symptom-based subtypes of depression and their psychosocial correlates: A person-centered approach focusing on the influence of sex

Stephanie Rodgers[a,*], Martin Grosse Holtforth[b], Mario Müller[a], Michael P. Hengartner[a], Wulf Rössler[a,c,d], Vladeta Ajdacic-Gross[1]

[a] Department of Psychiatry, Psychotherapy and Psychosomatics, Zurich University Hospital of Psychiatry, Switzerland

[b] Department of Psychology, University of Zurich, and Department of Psychology, University of Bern, Switzerland

[c] Collegium Helveticum, University of Zurich and Swiss Federal Institute of Technology, Zurich, Switzerland

[d] Institute of Psychiatry, Laboratory of Neuroscience (LIM 27), University of Sao Paulo, Brazil

* Corresponding author

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Abstract

Background:

Reducing the complexity of major depressive disorder by symptom-based subtypes constitutes the basis of more specific treatments. To date, few studies have empirically derived symptom subtypes separated by sex, although the impact of sex has been widely accepted in depression research.

Methods:

The community-based sample included 373 males and 443 females from the Zurich Program for Sustainable Development of Mental Health Services (ZInEP) manifesting depressive symptoms in the past 12 months. Latent Class Analysis (LCA) was performed separately by sex to extract sex-related depression subtypes. The subtypes were characterized by psychosocial characteristics.

Results:

Three similar subtypes were found in both sexes: a severe typical subtype (males: 22.8%; females: 35.7%), a severe atypical subtype (males: 17.4%; females: 22.6%), and a moderate subtype (males: 25.2%; females: 41.8%). In males, two additional subgroups were identified: a severe irritable/angry-rejection sensitive (IARS) subtype (30%) comprising the largest group, and a small psychomotor retarded subtype (4%). Males belonging to the severe typical subtype exhibited the lowest masculine gender role orientation, while females of the typical subtype showed more anxiety disorders. The severe atypical subtype was associated with eating disorders in both sexes and with alcohol/drug abuse/dependence in females. In contrast, alcohol/drug abuse/dependence was associated with the severe IARS subtype in males.

Limitations:

The study had a cross-sectional design, allowing for no causal inferences.

Conclusions:

This study contributes to a better understanding of sex-related depression subtypes, which can be well distinguished on the basis of symptom profiles. This provides the base for future research investigating the etiopathogenesis and effective treatment of the heterogeneous depression disorder.

Key words:

Depression; Subtypes; Sex; Epidemiology; Latent class analysis

Introduction

Growing dissatisfaction with the heterogeneity of major depressive disorder (MDD) has led researchers to search for specific depression subtypes of MDD that would facilitate the development of subtype-specific treatments (Baumeister and Parker, 2012). Robins and Guze (1970) emphasized the advantage of examining homogeneous subtypes in their classic paper as follows (McKay et al., 2004):

"Homogeneous diagnostic grouping provides the soundest base for studies of etiology, pathogenesis, and treatment. The roles of heredity, family interactions, intelligence, education, and sociological factors are most simply, directly, and reliably studied when the group studied is as homogeneous as possible" (p. 984).

The current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) allows for description of the symptom-based MDD subtypes melancholic, psychotic and atypical depression by specifiers (APA, 2013). Comorbidity is a further source of heterogeneity (Carragher et al., 2009). Hence, differentiation of heterogeneous depressive symptomatology and overlap with comorbid disorders/syndromes represent a major challenge for diagnostic classification.

Indicative person-centered methodological techniques such as latent class analysis (LCA) offer a promising statistical approach by extracting homogeneous subgroups of individuals based on their symptom profiles. The resultant depressive subtypes of the previous LCA subtyping studies vary between three (Carragher et al., 2009; Eaton et al., 1989; Lamers et al., 2012a; 2010), six (Sullivan et al., 1998), and seven (Kendler et al., 1996; Sullivan et al., 2002) latent classes. Not all of these LCA studies assessed the complete set of criteria for atypical depression. In addition, not all studies considered the variable sex, despite many research findings demonstrating the impact of sex on depression (Möller Leimkühler et al., 2004). For example, only two LCA studies in depression research to date have differentiated separate analyses by sex (Alexandrino-Silva et al., 2013; Crum et al., 2005). This lack of differentiation stands in contrast to the frequently voiced importance of analyses comparing population subgroups (e.g., Eaton et al., 1989).

Irrespective of the LCA findings, the repeatedly found higher rates of MDD in females (Kessler, 2003; Kessler et al., 1993; Weissman and Klerman, 1977) have been explained by the existence of the three subtypes atypical, anxious, and somatic depression, which are more prevalent in women and hence could form sex-preferred subtypes of MDD (Angst et al., 2002b; Clayton et al., 1991; Halbreich and Kahn, 2007; Silverstein, 1999, 2002). Overall, the focus has remained mostly on the situation of females, particularly outside the US (Möller Leimkühler et al., 2004).

Nevertheless, researchers and clinicians have speculated about a masculine subtype of MDD being defined by a distinct set of depressive symptoms (Cochran and Rabinowitz, 2000; Magovcevic and Addis, 2008; Rutz et al., 1995). One of the few measurements that aims at assessing a male depressive syndrome is the Gotland Scale of Male Depression, which defines male depression by symptoms such as irritability, restlessness, loss of self-control, alcohol or substance abuse and overwork. The existing definition and operationalization of the male depressive syndrome particularly needs to be validated in unbiased community samples and specified with respect to differential diagnoses (Möller Leimkühler et al., 2007).

Empirical evidence has demonstrated that not only sex but also gender, more specifically gender role orientation, has an impact on depression (Helgeson, 2005). Gender role orientation is a personality trait that an individual forms as member of a social system in which certain attributes and attitudes are stereotyped as masculine or feminine (Williams and Best, 1982). Two meta-reviews showed that masculine gender role orientation is a protective factor against depression, whereas feminine gender role orientation is unrelated to depression (Helgeson, 2005). To our knowledge, no study has examined whether gender role orientation differs between empirically derived depressive symptom subtypes.

The first aim of this study was to derive depressive subtypes separately for males and females by performing LCAs to a community sample. The second aim was to characterize the resultant subtypes by psychosocial correlates, such as demographic features, gender role orientation, male depressive syndrome, and comorbid disorders. Our main expectations were to find (1) a typical and atypical subtype for both sexes, (2) a male-related subtype with a delimitable symptom profile, (3) higher scores for masculinity in non-severe depression subtypes, and (4) differing comorbidity profiles between depressed males and females. Beyond these expectations we had an exploratory strategy.

We assessed a wide range of depressive symptoms, including atypical depression, to potentially capture further sex-related depressive subtypes.

Methods

Sample and procedures

The data were derived from the epidemiology survey of the Zurich Program for Sustainable Development of Mental Health Services (ZInEP; German: ***Z****ürcher* ***I****mpulsprogramm zur* ***n****achhaltigen* ***E****ntwicklung der* ***P****sychiatrie*). The survey was conducted to generate comprehensive data about mental health in the general population of adults in the canton of Zurich (total population about 1.4 million). Methodologically, and regarding age and sex, the survey was designed as a cross-sectional sequel to the longitudinal Zurich Study (Angst et al., 2005). It consisted of three components: (a) a brief telephone screening, (b) a structured face-to-face-interview supplemented by self-report questionnaires, and (c) a longitudinal survey. The survey was carried out between August 2010 and September 2012. For more details see Ajdacic-Gross et al. (2013, in press).

A Computer Assisted Telephone Interview (CATI) was administered for the initial telephone screening. The CATI was conducted by a market and field research institute, with support from experienced associates of the Zurich University Hospital of Psychiatry. The records of the screening sample were taken from the communal public authority register of the canton of Zurich. The sample was confined to subjects with Swiss nationality aged between 20 and 41 y at the beginning of the study. In analogy to the age profile of the Zurich Study, the participants were randomly selected from 12 sex-birth-year subgroups. Initially, *n*=9829 screenings (males: 4920; females: 4909) representative of the canton of Zurich were carried out. In cases where the target person could be reached by telephone, the response rate was 73.9% (males: 70.6%; females: 77.6%). The overall response rate was 53.6%.

In the next step, we randomly selected subjects from the screening sample for a comprehensive semi-structured face-to-face-interview. To increase the probability of the occurrence of mental disorders, we applied a stratifying sampling procedure with 60% high-scorers (defined as above the

75th percentile of the global severity index (GSI) of the Symptom Checklist-27 (SCL-27) (Hardt et al., 2004)) and 40% low-scorers (defined by scores below the 75th percentile). The face-to-face interviews were administered either in the subjects' homes or at the research division of the Zurich University Hospital of Psychiatry. The interviews were conducted by 21 clinical psychologists who had been intensively trained in use of the instrument. Six of them accomplished 61% of all 1500 interviews. The research team and the interviewers met periodically for supervision, but also for the exchange of experiences in order to improve the survey instruments and interview procedures. In addition, quality assurance measures were performed periodically, based on various outcome parameters (interview duration, response patterns, return of checklists, positive answers regarding continuing participation, symptom load, and symptom patterns). In one single case, an interviewer had to be dismissed due to insufficient quality.

Of the 9829 subjects who had completed the screening, 66.3% were initially interested in a face-to-face interview. When asked for an appointment, 64.9% (males: 69.4%, females: 60.0%) actually showed up. The final sample included 1500 subjects. Similarly to the Zurich-Study, this sample was composed of six female (*n*=125, 22 years; *n*=125, 24 y; *n*=125, 29 y; *n*=125, 31 y; *n*=125, 36 y; *n*=125, 42 y) and six male subgroups (*n*=125, 21 years; *n*=125, 23 y; *n*=125, 28 y; *n*=125, 30 y; *n*=125, 35 y; *n*=125, 41 y). To consider supplemental issues, all participants completed additional self-report questionnaires. Overall, *n*=1179 complete questionnaires were returned, i.e., the refusal rate was 21.4% (males: 28.4%; females: 14.4%).

The study was approved by the Ethics Committee of the Canton of Zurich (KEK). After being extensively informed about study procedure and aims both verbally and in writing, the participants gave their written consent.

Measurements

Assessment of depressive symptoms and comorbid disorders

The computer-assisted Mini-SPIKE, a shortened form of the SPIKE (Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbances for Epidemiology – Version 10) was used. The latter instrument was developed in the Zurich Study (Angst et al., 1984; 2005) and encompasses most common psychopathological syndromes/disorders and their social

consequences. According to DSM-III-R/IV criteria, axis I diagnoses were assessed for the time-period of the past twelve months (APA, 1987, 2000). As an exception, the neurasthenia diagnosis was based on ICD-10 criteria (WHO, 1992). Psychosis syndromes were computed using the schizophrenia nuclear symptoms (SNS) and schizotypal signs (STS) subscales (Rössler et al., 2007) derived from the SCL-90-R (Derogatis, 1977).

Validity and reliability of the SPIKE have previously been established for the assessment of depression and anxiety (Angst et al., 2005). The inter-rater reliability of the SPIKE was high, with kappas of 0.90 for the syndromal diagnosis. The SPIKE rating was found to have high sensitivity and modest specificity (0.95 and 0.59, respectively) for detecting depression at the diagnostic level and good sensitivity with respect to the sub-threshold level (Angst et al., 2005).

For the current study, analyses were carried out using the data from the face-to-face-interviews. The analyses were restricted to respondents who affirmed either the first or second filter question of the Mini-SPIKE section for depression. The selected indicators were 17 depressive symptoms (binary coded items: 'Symptom existent during the past twelve months?' 0= "no"; 1= "yes") comprising the nine DSM-IV 'A' criteria for major depression. Furthermore, we included three additional symptoms 'mood reactivity', 'hypersensitivity to critical remarks' (assessing rejection sensitivity), and 'irritable/angry' due to the potential impact of these criteria regarding atypical features (Halbreich and Kahn, 2007). A visual analog measure of subjective distress included in the Mini-SPIKE section for depression was used to complement the assessment of depression. This continuous scale is ranged from 0 to 100, with 0 indicating no distress (impairment) and 100 representing maximal distress (impairment).

Self-report instruments

To characterize the latent classes, we drew information from the following three instruments:

- The Bem Sex Role Inventory (BSRI) measures Masculinity and Femininity as two independent dimensions and operationalizes Androgyny as the difference between the two scales (Bem, 1974). The German adaptation of the BSRI consists of 60 items describing personality attributes. Participants are asked to judge how much a characteristic applies to him/herself. Each item is rated on a 7-point scale, ranging from 1 "never or hardly ever" to 7 "always". The reliabilities (internal consistency) obtained

with the German translation are sufficiently high. Moreover, the criterion validity, analyzed on the basis of the biological sex, is also acceptable (Schneider-Düker and Kohler, 1988).

- The Gotland Scale of Male Depression (Rutz, 1999; Rutz et al., 1995; Walinder and Rutz, 2001) consists of 13 items rated on a 4-point Likert scale (0= "not present" to 3="present to a high degree"), resulting in a possible total score range of 0-39. Based on their total score, subjects can be classified with the following tripartite standardization: 0-12="No signs of depression"; 13-26="Depression possible. Specific therapy, including psychopharmacological, possibly indicated"; 27-39="Clear signs of depression. Specific therapy, including psychopharmacological, clearly indicated". The male depressive syndrome was assessed retrospectively for the time-period of the past twelve months. The Gotland Scale has been validated in a number of studies and exhibits an adequate reliability and validity (Bech, 2001; Innamorati et al., 2011; Möller Leimkühler et al., 2007; Zierau et al., 2002). However, some authors have raised concerns regarding the psychometric criteria of this measure (Magovcevic and Addis, 2008).
- The German translation of the Assessment of DSM-IV Personality Disorders Questionnaire (ADP-IV) (Doering et al., 2007; Schotte and de Doncker, 1994) comprises 94 items, each rated on a 7-point Likert scale ranging from "totally disagree" to "totally agree". The items represent the 80 criteria of the 10 Axis II DSM-IV personality disorders, and, furthermore, 14 research criteria of the depressive and passive-aggressive personality disorders. Apart from a dimensional trait-score this instrument may serve as an initial screening instrument to suggest categorical diagnoses for single DSM-IV personality disorders. The ADP-IV shows a good differential validity and concordance with the SCID-II semi-structured interview (Schotte et al., 2004).

Statistical analysis

Latent Class Analysis

LCA was used to empirically identify sex-related subtypes of depressive syndromes. Person-centered approaches such as LCA aim to group individuals into homogeneous categories. In this manner, a yet

unobserved population heterogeneity may be captured by qualitatively or quantitatively differentiating subpopulations, or latent classes (Lubke and Muthén, 2005).

The most commonly used statistical fit indices are the Akaike information criterion (AIC; Akaike, 1987), the Bayesian information criterion (BIC; Schwarz, 1978), the sample-size adjusted BIC (ABIC; Sclove, 1987), (Nylund et al., 2007), and the entropy measure. The lower the values of the AIC, BIC and ABIC, the better the model fit. The entropy index (range from 0 to 1) measures the precision of classification. High values indicate distinct classes. Based on an extension of a theorem by Vuong (1989), the Lo-Mendell-Rubin likelihood ratio test (LMR-LRT) (Lo et al., 2001) compares a model with k classes compared to a model with k-1 classes (Nylund et al., 2007). Of all above mentioned model fit indices, the BIC provided the most reliable measure in a simulation study (Nylund et al., 2007). However, only the consideration of fit indices in combination with the theoretical interpretability and appropriateness of a given class solution should guide the final selection (Muthén, 2004).

To determine the optimal number of latent classes in the final model, one to six latent class models were fitted to the data. To avoid problems concerning local maxima, the number of random starts was set to 5000 for the first step, using the 500 best solutions in the final calculation.

After the model fit indices of the unconditional models were examined, they were compared with the indices derived from the conditional models, computed by inclusion of the covariate sex. Finally, LCAs were applied separately for males and females.

LCAs were performed using Mplus version 7 for Macintosh (Muthén and Muthén, 1998-2012). To characterize the latent classes by psychosocial correlates, chi-square tests, Fisher's exact tests, Kruskal-Wallis tests, and multinomial logistic regressions (odds ratios (OR) with 95% confidence intervals [CI]) using the latent classes as dependent variable and the psychosocial correlates as independent variables were computed using SPSS statistics version 20 (SPSS Inc., USA). In order to account for the stratification of our sample, we included the stratification variable (high-low scorers status, cut-off criterion 75th percentile of the GSI of the SCL-27 (Hardt et al., 2004)) as independent variable in the multinomial logistic regressions.

Results

Descriptive statistics

The absolute and relative frequencies of the depressive symptoms separated for males and females are displayed in Table 1.

Table 1. Frequencies of depressive symptoms for males (*n*=373) and females (*n*=443)

Depressive symptom	Males n (%)	Females n (%)
Depressed mood	298 (80.1%)	400 (90.7%)
Anhedonia, loss of interest/activity	354 (94.9%)	394 (88.9%)
Fatigue, loss of energy	335 (89.8%)	404 (91.2%)
Psychomotor retardation	83 (22.3%)	93 (21.0%)
Psychomotor agitation	114 (30.7%)	138 (31.2%)
Insomnia	188 (50.5%)	232 (52.4%)
Hypersomnia	111 (29.8%)	146 (33.0%)
Loss of weight	40 (10.8%)	74 (16.7%)
Gain in weight	43 (11.5%)	73 (16.5%)
Loss of appetite	139 (37.3%)	151 (34.1%)
Increased appetite	76 (20.5%)	118 (26.7%)
Irritable, angry	255 (68.4%)	316 (71.5%)
Hypersensitivity to critical remarks	238 (63.8%)	306 (69.1%)
Feelings of inferiority, self-reproaches, loss of self-confidence, guilt	296 (79.4%)	348 (78.6%)
Concentration/memory problems, difficulties in decision making	306 (82.0%)	355 (80.1%)
Taedium vitae, suicidal thoughts/attempt	113 (30.3%)	115 (26.0%)
Mood reactivity	311 (84.1%)	356 (80.7%)

Model selection

Routinely, six latent class models were fitted to the data with an increasing number of classes, i.e. for the overall data (with and without the covariate sex) and separately for males and females. The three and five class solutions indicated the best fit to the data for both overall models. Inclusion of the covariate sex demonstrated significant sex-differences with respect to the latent classes (for more details see the last paragraph of the 'Symptom profiles' section below).

Table 2 compares the resulting model fit indices for males and females, from the one-class model through to the six-class model. For males, the BIC was smallest in the two-class model, whereas the five-class model yielded the lowest AIC and ABIC. The LMR-LRT showed significant *p* values for both the two-class and five-class models, and hence confirmed the improvement of these models over a one and four-class model, respectively. The plotted estimated symptom probabilities demonstrated

that the two-class model mainly differed between low scorers and high scorers. In contrast, the five-class solution shared more similarities with common (atypical and typical) depressive subtypes. Therefore, we chose the five-class model. For females, the BIC and ABIC showed that the three or four-class solution provided the best fit to the data, though the LMR-LRT was only significant for the two-class model. After comparison of the plots the three-class solution was chosen, as the four-class solution merely produced a further moderate class of doubtful meaning.

Table 2. Model fit indices derived from latent class analysis with classes ranging from 1 to 6 for males (*n*=373) and females (*n*=443) with depressive symptoms

Fit statistics	1-class	2-class	3-class	4-class	5-class	6-class
Males						
AIC	6480.529	6241.272	6181.232	6151.938	6130.679	6135.908
BIC	6547.196	6378.527	6389.076	6430.370	6479.700	6555.517
ABIC	6493.260	6267.482	6220.922	6205.108	6197.329	6216.037
Entropy	N/A	.815	.776	.773	.816	.817
LMR-LRT, adj.	N/A	$p < .001$	$p = .1318$	$p = .2284$	$p < .05$	p= .8946
Females						
AIC	7854.477	7508.829	7424.715	7404.879	7388.850	7378.244
BIC	7924.068	7652.104	7641.674	7695.523	7753.177	7816.256
ABIC	7870.117	7541.029	7473.476	7470.201	7470.731	7476.686
Entropy	NA	.686	.712	.747	.781	.751
LMR-LRT, adj.	NA	$p < .001$	$p = .0764$	$p = .0890$	$p = .1253$	p= .3924

Bayesian Information Criterion (BIC), Sample-Size adjusted Bayesian Information Criterion (ABIC), Lo-Mendell-Rubin likelihood ratio test, adjusted (LMR-LRT adj.)
NA, not applicable.

Symptom profiles

Males

Fig. 1 (top) depicts the estimated probabilities of the five-class model for the subgroup of males. Subjects in class one endorsed high probabilities of most depressive symptoms, apart from the weight-related symptoms. This class was notably characterized by high probabilities of irritability/anger and hypersensitivity to critical remarks. Although these symptoms are commonly associated with atypical depression, further atypical criteria such as weight gain and increased appetite were lacking in class one. Therefore, class one was labeled 'irritable/angry-rejection sensitive (IARS)'. The second class included individuals with high probabilities of experiencing increased appetite, weight gain and hypersensitivity to critical remarks. Due to its atypical symptom profile, class two was labeled 'atypical'. In contrast, class three was labeled 'typical' because it was characterized by typical symptoms such as loss of appetite and weight. Compared to classes one to three, subjects in class four experienced less depressed mood, although the probability of

anhedonia was comparable. Additionally, class four was characterized by a high probability of psychomotor retardation, insomnia plus concentration and memory problems, but no loss of self-confidence/guilt. This class was labeled 'psychomotor retarded'. Finally, individuals of class five exhibited low probabilities for all symptoms, hence this class was labeled 'moderate'. Based on the visual analog measure of subjective distress, classes one to three showed the highest subjective burden of depressive symptoms (mean values: IARS=66.69; atypical=69.31; typical=72.45; psychomotor retarded=53.00; moderate=51.00). The group differences were significant (Kruskal-Wallis test $p< .001$; data not tabulated). Consequently, we additionally labeled subtypes one to three 'severe'.

Females

The three-class solution for females is shown in Fig. 1 (below). Subjects in class one were more likely to manifest symptoms such as weight gain and increased appetite apart from the two main depression symptoms, i.e., depressed mood and anhedonia. Due to its atypical symptom pattern, this class was labeled 'atypical'. Class two presented a symptom pattern marked by both loss of weight and appetite. Because this class was characterized by typical depressive symptoms, it was labeled 'typical'. Finally, the symptom probabilities of class three were less pronounced for all depressive symptoms (apart from the symptom mood reactivity). Hence, this class was labeled 'moderate'. Both classes 'atypical' and 'typical' had significantly higher values on the visual analog measure of subjective distress than the moderate class (mean values: atypical=75.15; typical=75.19; moderate=62.45, Kruskal-Wallis test $p<.001$; data not tabulated). For this reason, we added the term 'severe' to their label.

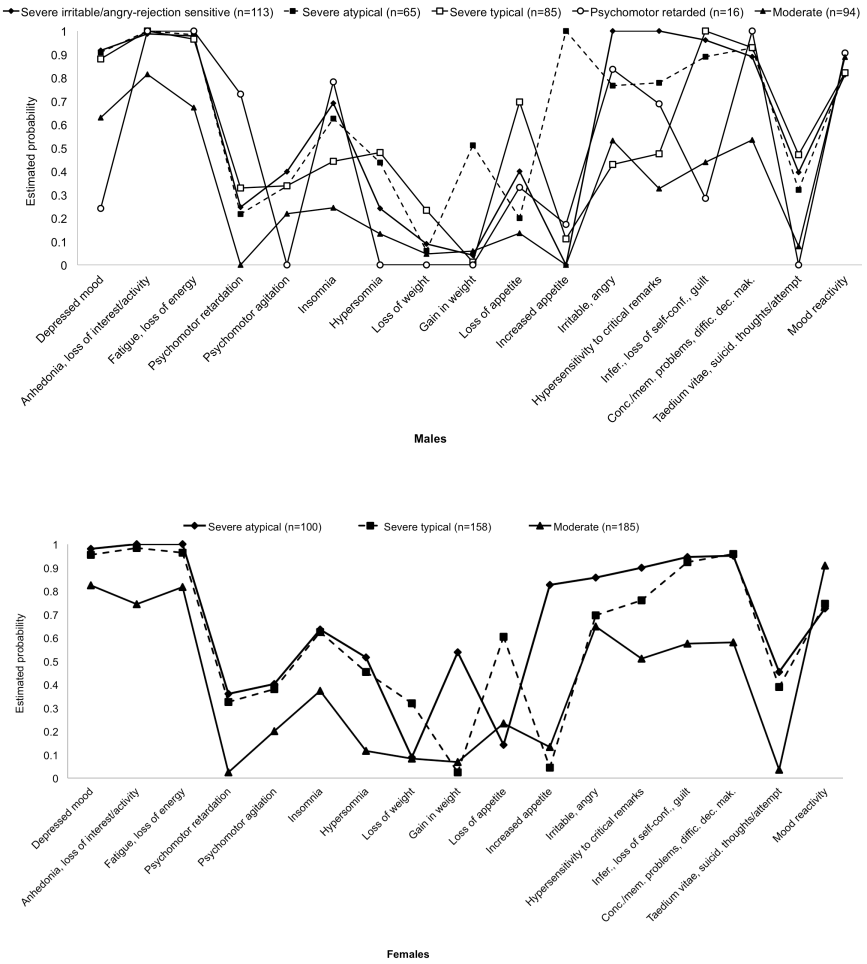

Fig. 1. Symptom probability plots for males (*n*=373), and females (*n*=443)

Aggregated items: loss of pleasure, loss of interest/activity; fatigue, loss of energy; loss of self-confidence, feelings of inferiority, self-reproaches, guilt; difficulties in decision making, concentration/memory problems; taedium vitae, suicidal thoughts/attempt;
Disaggregated items: appetite loss/gain; weight loss/gain; insomnia/hypersomnia; psychomotor agitation/retardation.

Additional analyses showed that the three-class latent class model with inclusion of the covariate sex had a significantly higher risk for females of being either in the severe atypical class (OR=2.0, CI=1.4–3.0) and the moderate class (OR=1.6, CI=1.2–2.2) compared to the severe typical class. Unexpectedly, males showed a significantly higher risk of being in the severe typical class (OR=1.6, CI=1.2–2.2) than in the moderate class (not tabulated).

Psychosocial correlates

Males

Table 3 displays the psychosocial characteristics for males of the five latent classes identified. Both gender role orientation and male depressive syndrome differed significantly between the latent classes. In terms of psychiatric diagnoses, the following diagnoses showed significant differences: major depression, hypomania/mania, generalized anxiety disorder, simple phobia, social phobia, binge eating, and personality disorders. The proportion of low-scorers was significantly higher in the moderate class than in class one to three.

Table 3. Psychosocial characteristics for the five latent classes for the subsample of males (*n*=373)

	Latent Classes					
Correlates [a]	**Class 1 Severe IARS *n*=113 % (*n*)**	**Class 2 Severe atypical *n*=65 % (*n*)**	**Class 3 Severe typical *n*=85 % (*n*)**	**Class 4 Psychomotor retarded *n*=16 % (*n*)**	**Class 5 Moderate *n*=94 % (*n*)**	**Chi²/F-Test (two-tailed)**
Age						*p*=.163
21	30.3 (20)	10.6 (7)	21.2 (14)	3.0 (2)	34.8 (23)	
23	25.0 (17)	25.0 (17)	17.6 (12)	1.5 (1)	30.9 (21)	
28	32.8 (20)	14.8 (9)	34.4 (21)	4.9 (3)	13.1 (8)	
30	27.1 (16)	16.9 (10)	27.1 (16)	3.4 (2)	25.4 (15)	
35	26.2 (16)	18.0 (11)	21.3 (13)	8.2 (5)	26.2 (16)	
41	41.4 (24)	19.0 (11)	15.5 (9)	5.2 (3)	19.0 (11)	
Education						*p*=.305
<High school diploma	31.0 (49)	21.5 (34)	22.8 (36)	3.8 (6)	20.9 (33)	
≥High school diploma	29.8 (64)	14.4 (31)	22.8 (49)	4.7 (10)	28.4 (61)	
Urbanicity						*p*=.750
Urban (Zurich, Winterthur)	30.1 (71)	16.1 (38)	22.9 (54)	3.8 (9)	27.1 (64)	
Rural (otherwise)	30.7 (42)	19.7 (27)	22.6 (31)	5.1 (7)	21.9 (30)	
Gender role orientation						*p*<.05 [II, VIII, IX]
Masculine	36.4 (24)	12.1 (8)	7.6 (5)	7.6 (5)	36.4 (24)	
Feminine	31.2 (10)	18.8 (6)	34.4 (11)	0.0 (0)	15.6 (5)	
Androgynous	29.2 (14)	16.7 (8)	25.0 (12)	2.1 (1)	27.7 (13)	
Undifferentiated	24.2 (15)	17.7 (11)	30.6 (19)	6.5 (4)	21.0 (13)	
Male depressive syndrome (past year)						*p*<.001 [IV, VII, IX]
No signs of depression	26.0 (34)	10.7 (14)	19.1 (25)	5.3 (7)	38.9 (51)	
Depression possible	37.3 (31)	22.9 (19)	30.1 (25)	3.6 (3)	6.0 (5)	
Clear signs of depression	41.7 (5)	25.0 (3)	33.3 (4)	0.0 (0)	0.0 (0)	
Comorbid psychiatric disorder/syndrome (past year)						
MDD [b]	35.2 (43)	20.5 (25)	33.6 (41)	2.5 (3)	8.2 (10)	*p*<.001 [IV, VII, IX, VIII]
DYST [b]	23.5 (4)	23.5 (4)	47.1 (8)	0.0 (0)	5.9 (1)	*p*=.084
Hypomania/ mania [c]	50.0 (14)	25.0 (7)	7.1 (2)	0.0 (0)	17.9 (5)	*p*<.05 [II]
Bipolar disorder [d]	44.4 (4)	33.3 (3)	22.2 (2)	0.0 (0)	0.0 (0)	*p*=.268
Neurasthenia [e, f]	38.9 (14)	11.1 (4)	27.8 (10)	8.3 (3)	13.9 (5)	*p*=.139
GAD [g]	41.7 (15)	30.6 (11)	19.4 (7)	2.8 (1)	5.6 (2)	*p*<.01 [IV, VII]
Simple Phobia [c]	31.5 (17)	27.8 (15)	20.4 (11)	11.1 (6)	9.3 (5)	*p*<.01 [IV, VII, X]
Agoraphobia [c]	35.3 (6)	29.4 (5)	23.5 (4)	5.9 (1)	5.9 (1)	*p*=.219
Social phobia [c]	44.7 (21)	14.9 (7)	29.8 (14)	4.3 (2)	6.4 (3)	*p*<.01 [IV, VII, IX]
OCD [c]	41.7 (15)	16.7 (6)	16.7 (6)	0.0 (0)	25.0 (9)	*p*=.481
Panic disorder [c]	40.0 (8)	15.0 (3)	30.0 (6)	0.0 (0)	15.0 (3)	*p*=.500
Psychosis syndromes [h]	25.8 (8)	25.8 (8)	35.5 (11)	0.0 (0)	12.9 (4)	*p*=.127
Bulimia [b, c]	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	--
Binge eating [b, c, i]	17.2 (5)	41.4 (12)	20.7 (6)	6.9 (2)	13.8 (4)	*p*<.01 [I, VII]
Anorexia [b]	25.0 (1)	50.0 (2)	25.0 (1)	0.0 (0)	0.0 (0)	*p*=.419
Alcohol abuse/dependence [c]	39.5 (30)	19.7 (15)	17.1 (13)	0.0 (0)	23.7 (18)	*p*=.061
Drug abuse/dependence [j]	38.1 (16)	19.0 (8)	23.8 (10)	2.4 (1)	16.7 (7)	*p*=.623
Any personality disorder [c, k]	27.3 (3)	54.5 (6)	9.1 (1)	9.1 (1)	0.0 (0)	*p*<.01 [VII]
Suicidality [l]	20.0 (1)	40.0 (2)	40.0 (2)	0.0 (0)	0.0 (0)	*p*=.213
Sample stratification[m]						*p*<.001 [III, IV, VII, IX]
Low scorers	16.7 (13)	15.4 (12)	12.8 (10)	6.4 (5)	48.7 (38)	
High scorers	33.9 (100)	18.0 (53)	25.4 (75)	3.7 (11)	19.0 (56)	

IARS, irritable/angry-rejection sensitive; MDD, major depression disorder; DYST, dysthymia; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; [I] Class 1 significantly differs from class 2; [II] Class 1 significantly differs from class 3; [III] Class 1 significantly differs from class 4; [IV] Class 1 significantly differs from class 5; [V] Class 2 significantly differs from class 3; [VI] Class 2 significantly differs from class 4; [VII] Class 2 significantly differs from class 5; [VIII] Class 3 significantly differs from class 4; [IX] Class 3 significantly differs from class 5; [X] Class 4 significantly differs from class; [a] The discrepancy between the total number of persons and the number of persons in the following rows result from missing items; [b] DSM-III-R; [c] DSM-IV; [d] Def. BRIDGE Study (Angst et al., 2011); [e] ICD-10; [f] 3 month criteria; [g] DSM-III; [h] Disorders of form of thought, derealization, depersonalization, delusion, disorder of ego-boundary, hallucinations, paranoia syndrome; [i] including binge eating symptoms; [j] Defined as subjective burden >=50, assessed using a visual analog scale (range 0-100: 0: no burden, 100 maximal burden); [k] Paranoid, schizotypal, avoidant, dependent, obsessive-compulsive, borderline, histrionic, narcissistic, depressive; [l] Suicide attempt; [m] Cut-off criterion: 75th percentile of the global severity index (GSI) of the Symptom Checklist-27 (SCL-27) (Hardt et al., 2004).

In Table 4, multivariate logistic regression analyses were performed, treating the moderate subtype as reference class. Due to the small class size of the psychomotor retarded class, we excluded it from this analysis. Having a pronounced masculine gender role orientation was associated with a decreased risk of being in the severe typical class. The odds of having any affective disorder were 8.4 fold higher in the severe IARS class, 7.8 fold higher in the severe atypical class, and 7.7 fold higher in the severe typical class compared to the moderate class. Anxiety disorders were significantly associated with both the severe IARS class and the severe atypical class. Alcohol/drug abuse/dependence, age and rural residence were associated with the severe IARS class. The risk of having an eating disorder was associated particularly with the severe atypical subtype. Finally, there were significantly fewer low-scorers than high-scorers in the severe IARS class and the severe typical class.

Table 4. Odds ratios and confidence intervals (95%) from multivariate multinomial logistic regressions for the five latent classes for males (*n*=373)

	Latent Classes		
	Severe irritable/angry-rejection sensitive (IARS) vs. moderate (ref.)	**Severe atypical vs. moderate (ref.)**	**Severe typical vs. moderate (ref.)**
Age			
21	0.28 (0.05–1.49)	0.27 (0.04–1.79)	1.36 (0.21–8.71)
23	0.42 (0.08–2.26)	0.30 (0.05–2.02)	0.76 (0.11–5.45)
28	0.46 (0.09–2.37)	0.47 (0.08–2.87)	1.69 (0.29–10.04)
30	0.34 (0.07–1.69)	0.31 (0.05–1.92)	1.91 (0.32–11.35)
35	0.20 (0.04–0.93)*	0.42 (0.08–2.09)	0.74 (0.13–4.11)
41 (ref.)	--	--	--
Education			
<High school diploma	1.84 (0.64–5.24)	2.25 (0.70–7.23)	1.19 (0.39–3.61)
≥High school diploma (ref.)	--	--	--
Urbanicity			
Rural (otherwise)	4.04 (1.33–12.28)*	1.87 (0.52–6.69)	2.95 (0.93–9.34)
Urban (Zurich, Winterthur) (ref.)	--	--	--
Gender role orientation			
Masculine	1.69 (0.50–5.63)	0.50 (0.13–1.94)	0.18 (0.05–0.69)**
Feminine	3.41 (0.72–16.22)	1.95 (0.38–10.14)	2.07 (0.47–9.07)
Androgynous	1.40 (0.36–5.37)	0.69 (0.16–2.98)	0.91 (0.25–3.30)
Undifferentiated (ref.)	--	--	--
Comorbid psychiatric disorder/syndrome (lifetime)			
Any affective disorder	8.37 (2.67–26.26)***	7.80 (2.22–27.38)**	7.72 (2.30–25.85)**
Any anxiety disorder	3.37 (1.17–9.72)*	4.44 (1.41–14.04)**	1.71 (0.56–5.17)
Alcohol/drug abuse/dependence	2.97 (0.99–8.89)*	1.57 (0.44–5.64)	1.31 (0.40–4.26)
Eating disorders	2.17 (0.24–20.07)	11.10 (1.46–84.37)*	2.35 (0.25–22.00)
Sample stratification			
Low scorers	0.15 (0.04–0.49)**	0.39 (0.11–1.36)	0.13 (0.03–0.53)**
High scorers (ref.)	--	--	--

ref: reference

Affective disorders: MDD, dysthymia, hypomania, mania, bipolar disorder, neurasthenia; anxiety disorders: agoraphobia, obsessive-compulsive disorder, simple phobia, panic disorder, generalized anxiety disorder, social phobia; eating disorders: binge eating, anorexia

Note: The psychomotor retarded class was excluded for the multivariate analyses due to the small number of subjects; the male depressive syndrome was excluded for reasons of multicollinearity; multivariate analyses regarding the psychosis syndrome and personality disorders were not feasible because of small cell sizes.

*p<.05.

**p<.01.

***p<.001.

Females

The psychosocial characteristics of the three latent classes derived from the female subsample are presented in Table 5. The low vs. high scorers status and the male depressive syndrome differentiated between the latent classes. Apart from simple phobia, bulimia, anorexia, and drug abuse/dependence, all 12-month diagnoses/syndromes significantly differed between the classes.

Table 5. Psychosocial characteristics for the three latent classes for the subsample of females (*n*=443)

	Latent Classes			
Correlates [a]	**Class 1 Severe atypical *n*=100 % (*n*)**	**Class 2 Severe typical *n*=158 % (*n*)**	**Class 3 Moderate *n*=185 % (*n*)**	**Chi²/F-Test (two-tailed)**
Age				*p*=.480
22	17.7 (14)	32.9 (26)	49.4 (39)	
24	25.0 (18)	38.9 (28)	36.1 (26)	
29	21.5 (17)	38.0 (30)	40.5 (32)	
31	21.4 (15)	28.6 (20)	50.0 (35)	
36	23.7 (18)	32.9 (25)	43.4 (33)	
42	26.9 (18)	43.3 (29)	29.9 (20)	
Education				*p*=.059
<High school diploma	22.7 (39)	41.9 (72)	35.5 (61)	
≥High school diploma	22.5 (61)	31.7 (86)	45.8 (124)	
Urbanicity				*p*=.690
Urban (Zurich, Winterthur)	21.3 (56)	36.9 (97)	41.8 (110)	
Rural (otherwise)	24.4 (44)	33.9 (61)	41.7 (75)	
Gender role orientation				*p*=.471
Masculine	25.0 (11)	29.5 (13)	45.5 (20)	
Feminine	19.3 (21)	42.2 (46)	38.5 (42)	
Androgynous	23.6 (17)	27.8 (20)	48.6 (35)	
Undifferentiated	22.9 (19)	39.8 (33)	37.3 (31)	
Male depressive syndrome (past year)				*p*<.001 [II, III]
No signs of depression	16.8 (26)	22.6 (35)	60.6 (94)	
Depression possible	21.6 (29)	47.0 (63)	31.3 (42)	
Clear signs of depression	33.3 (11)	66.7 (22)	0.0 (0)	
Comorbid psychiatric disorder/syndrome (past year)				
MDD [b]	33.5 (52)	47.1 (73)	19.4 (30)	*p*<.001 [II, III]
DYST [b]	50.0 (8)	37.5 (6)	12.5 (2)	*p*<.05 [II]
Hypomania/ mania [c]	50.0 (15)	36.7 (11)	13.3 (4)	*p*<.001 [I, II, III]
Bipolar disorder [d]	56.2 (9)	43.8 (7)	0.0 (0)	*p*<.001 [II, III]
Neurasthenia [e, f]	36.5 (23)	49.2 (31)	14.3 (9)	*p*<.001 [II, III]
GAD [g]	28.3 (17)	53.3 (32)	18.3 (11)	*p*<.001 [II, III]
Simple Phobia [c]	24.4 (20)	43.9 (36)	31.7 (26)	*p*=.054
Agoraphobia [c]	34.6 (9)	50.0 (13)	15.4 (4)	*p*<.05 [II, III]
Social phobia [c]	38.3 (23)	41.7 (25)	20.0 (12)	*p*<.001 [II, III]
OCD [c]	24.5 (12)	55.1 (27)	20.4 (10)	*p*<.01 [III]
Panic disorder [c]	35.7 (10)	46.4 (13)	17.9 (5)	*p*<.05 [II, III]
Psychosis syndromes [h]	31.6 (12)	60.5 (23)	7.9 (3)	*p*<.001 [II, III]
Bulimia [b, c]	50.0 (3)	33.3 (2)	16.7 (1)	*p*<.144
Binge eating [b, c, i]	51.2 (21)	26.8 (11)	22.0 (9)	*p*<.001 [I, II]
Anorexia [b]	0.0 (0)	0.0 (0)	100.0 (2)	*p*=.512
Alcohol abuse/dependence [c]	40.0 (8)	50.0 (10)	10.0 (2)	*p*<.01 [II, III]
Drug abuse/dependence [j]	37.9 (11)	34.5 (10)	27.6 (8)	*p*=.090
Any personality disorder [c, k]	23.1 (6)	57.7 (15)	19.2 (5)	*p*<.05 [III]
Suicidality [l]	50.0 (3)	50.0 (3)	0.0 (0)	*p*<.01 [II, III]
Sample stratification [m]				*p*<.001 [II, III]
Low scorers	9.0 (10)	22.5 (25)	68.5 (76)	
High scorers	27.1 (90)	40.1 (133)	32.8 (109)	

MDD, major depression disorder; DYST, dysthymia; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder

[I] Class 1 significantly differs from class 2; [II] Class 1 significantly differs from class 3; [III] Class 2 significantly differs from class 3

[a] The discrepancy between the total number of persons and the number of persons in the following rows result from missing items; [b] DSM-III-R; [c] DSM-IV; [d] Def. BRIDGE Study (Angst et al., 2011); [e] ICD-10; [f] 3 month criteria; [g] DSM-III; [h] Disorders of form of thought, derealization, depersonalization, delusion, disorder of ego-boundary, hallucinations, paranoia syndrome; [i] including binge eating symptoms; [j] Defined as subjective burden >=50, assessed using a visual analog scale (range 0-100: 0: no burden, 100 maximal burden); [k] Paranoid, schizotypal, avoidant, dependent, obsessive-compulsive, borderline, histrionic, narcissistic, depressive; [l] Suicide attempt; [m] Cut-off criterion: 75th percentile of the global severity index (GSI) of the Symptom Checklist-27 (SCL-27) (Hardt et al., 2004).

Table 6 displays odds ratios and confidence intervals (95%) for the three latent classes, with the moderate class utilized as reference class. The following differences in demographic correlates were observed: females at age 31 were less likely to be members of the severe typical class. Furthermore, females with less than a high school diploma belonged significantly more often to the severe typical class. Beyond these demographic characteristics, the three subtypes showed significant differences with respect to comorbid diagnoses. Having a diagnosis of any affective disorder was associated with both severe subtypes. However, only the severe typical subtype showed more anxiety disorders. In contrast, the severe atypical class was significantly associated with alcohol/drug abuse/dependence, eating disorders, and less low-scorers compared to the moderate class. With regard to eating disorders, the opposite effect was observed for the severe typical class.

Table 6. Odds ratios and confidence intervals (95%) from multivariate multinomial logistic regressions for the three latent classes for females (*n*=443)

	Latent Classes	
	Severe atypical vs. moderate (ref.)	**Severe typical vs. moderate (ref.)**
Age		
22	0.29 (0.08–1.07)	0.47 (0.16–1.39)
24	0.87 (0.25–2.95)	0.83 (0.28–2.50)
29	0.50 (0.15–1.64)	0.54 (0.19–1.52)
31	0.33 (0.10–1.11)	0.30 (0.10–0.89)*
36	0.57 (0.18–1.82)	0.37 (0.13–1.05)
42 (ref.)	--	--
Education		
<High school diploma	1.55 (0.74–3.25)	2.07 (1.11–3.85)*
≥High school diploma (ref.)	--	--
Urbanicity		
Rural (otherwise)	1.03 (0.48–2.19)	1.17 (0.61–2.25)
Urban (Zurich, Winterthur) (ref.)	--	--
Gender role orientation		
Masculine	1.29 (0.44–3.78)	0.90 (0.34–2.37)
Feminine	1.24 (0.51–3.03)	1.50 (0.70–3.18)
Androgynous	1.34 (0.50–3.55)	0.78 (0.32–1.86)
Undifferentiated (ref.)	--	--
Comorbid psychiatric disorder/syndrome (lifetime)		
Any affective disorder	3.07 (1.53–6.16)**	2.56 (1.37–4.77)**
Any anxiety disorder	0.78 (0.38–1.61)	2.61 (1.43–4.76)**
Psychosis syndromes	2.43 (0.55–10.83)	2.91 (0.73–11.53)
Alcohol/drug abuse/dependence	3.83 (1.27–11.58)*	2.23 (0.77–6.52)
Eating disorders	3.20 (1.10–9.34)*	0.26 (0.07–0.98)*
Any personality disorder	1.32 (0.33–5.32)	1.59 (0.43–5.80)
Sample stratification		
Low scorers	0.12 (0.04–0.37)***	0.58 (0.29–1.16)
High scorers (ref.)	--	--

ref: reference

Affective disorders: MDD, dysthymia, hypomania, mania, bipolar disorder, neurasthenia; anxiety disorders: agoraphobia, obsessive-compulsive disorder, simple phobia, panic disorder, generalized anxiety disorder, social phobia; psychosis syndromes: disorders of form of thought, derealization, depersonalization, delusion, disorder of ego-boundary, hallucinations, paranoia syndrome; eating disorders: bulimia, binge eating, anorexia; personality disorders: Paranoid, schizotypal, avoidant, dependent, obsessive-compulsive, borderline, histrionic, narcissistic, depressive

Note: The male depressive syndrome was excluded for reasons of multicollinearity; multivariate analyses regarding suicidality were not feasible because of small cell sizes

*p<.05; **p<.01; ***p<.001.

Discussion

The main purpose of the current study was to apply a person-centered methodological approach to a community sample in order to derive a sex-related typology of depressive syndromes and to characterize the resulting subtypes by psychosocial correlates including gender issues. To our knowledge, this is the first community-based study investigating sex-related depressive subtypes from this point of view. Our findings indicated both similarities and differences in the patterns of depressive symptoms between males and females. Whereas in both sexes, severe typical (males: 22.8%; females: 35.7%), severe atypical (males: 17.4%; females: 22.6%), and moderate (males: 25.2%; females: 41.8%) subtypes could be identified, two additional male-specific subgroups were detected: First, the severe IARS class, which was the largest group within males (30%), and second, the psychomotor retarded class comprising the smallest subgroup of males (4%).

Atypical and typical depression subtypes

The severe typical and severe atypical subtypes are in line with earlier LCA subtyping studies (Kendler et al., 1996; Lamers et al., 2012a; 2010; Sullivan et al., 1998; 2002). Furthermore, these subtypes provide support for the DSM-5 specifiers melancholia and atypical depression (APA, 2013). Consequently, the existence of the typical and atypical subtype confirmed our a priori expectations.

The severe atypical subtype was twofold more prevalent among females than among males in our data. This is comparable to the known two- to fourfold higher prevalence rates of atypical depression in women (Angst et al., 2002b). With regard to the severe typical subtype, we surprisingly found a 1.6 higher risk for males than for females. Given that three recent studies also found higher prevalence rates of typical depressive symptoms (melancholia) in males (Angst et al., 2007; Hildebrandt et al., 2003; Xiang et al., 2012), this subtype seems to be a phenotype associated with the male sex. Apart from this subtype, we identified two further male-related subtypes, which will be discussed in the following section.

Male-specific subtypes: Severe irritable/angry-rejection sensitive and psychomotor retarded

In accordance with our initial assumption, we derived a male-specific subtype with a distinct symptom profile. With its association with more alcohol/drug abuse/dependence, the severe IARS subtype tentatively resembles Rutz's postulated male depressive syndrome (Rutz, 1999; Rutz et al., 1995; Walinder and Rutz, 2001). In addition, males belonging to the severe IARS subtype displayed the highest relative frequencies of a masculine gender role orientation compared to the other two severe classes, which is in theoretical line with the male depressive syndrome (Rutz et al., 1997). However, exploratory analyses showed that, despite Rutz's expectations, neither antisocial symptoms nor a diagnosis of antisocial personality disorder occurred more often in this class. The severe IARS subtype was adequately captured by the Gotland Scale, which assesses the male depressive syndrome. But also both non-sex-related severe typical and atypical subtypes were assessed by this scale. Thus, the findings of two recent studies showing that the Gotland Scale assesses male depression in both sexes (Innamorati et al., 2011; Möller Leimkühler and Yucel, 2010) could be replicated in our Swiss community sample. In addition, Möller Leimkühler (2007) emphasized the importance of clarifying the differential diagnosis of the male depressive syndrome and bipolar depression. In support of associations with bipolar depression, our analyses showed significantly higher rates of hypomania and mania for the male-related severe IARS class. This finding supports the assertion that this subtype is more strongly linked to bipolar than unipolar depression. In females, the same comorbid condition also occurred in the severe atypical subtype, as has previously been demonstrated in other studies (Angst et al., 2006; 2000b; Benazzi, 1999; Perugi et al., 1998). However if subjects fluctuate between typical and atypical episodes over time, cross-sectional sampling may lead to an overestimation of comorbidities such as bipolar disorders, at least with respect to atypical depression. In contrast, within longitudinally stable depression subtypes many comorbid conditions disappeared and the atypical subtype remained solely characterized by comorbid eating disorders (Levitan et al., 1997; Rodgers et al., 2013). This finding may also occur analogically in the severe IARS subtype. Hence, longitudinal replication is required to clarify the nature of this subtype as well as its potential confounding with bipolar syndromes.

The psychomotor retarded subtype showed a distinct symptom profile and was distinguishable from the other subtypes. We did not expect to find this subtype a priori, demonstrating the exploratory potential of the LCA approach. Because this subtype only comprised a small group of males in our data, it will not be discussed in detail. It should however be noted that the association of

psychomotor retardation with male depression has already been found in other studies (Sobin and Sackeim, 1997). Furthermore, a recent LCA study highlighted the discriminative power of psychomotor activity in differentiating the symptom subtypes within the subgroup of males (Alexandrino-Silva et al., 2013).

Psychosocial correlates

The second aim of the study was to test the validity of the resultant classes by examining differences in psychosocial constructs.

a) Gender role orientation

The consistent finding that masculinity acts as a protective factor against depression (Helgeson, 2005) (possibly explained by the mediating influence of subjective problem-solving abilities (Marcotte et al., 1999)), could not be adequately tested with our data because we only examined subjects manifesting depressive symptoms. However, due to the protective influence of masculinity we initially assumed that subjects within the moderate subtype would manifest higher scores of masculinity than the severe subtypes because they display a less severe depressive symptomatology. This was not the case for either sex. In fact, we did not observe any significant differences between the gender role orientations and the depression subtypes for females. On the other hand, we did find interesting differences within males: individuals belonging to the severe typical subtype displayed significantly lower scores in masculinity than all other subtypes. Hence, males with a 'non-masculine' gender role orientation seem to develop typical depression symptoms, while masculine males display depressive symptoms that may be more acceptable among their peers, such as irritability, anger, and substance abuse (Cochran and Rabinowitz, 2000; Wide et al., 2011). Because this is the first study investigating the associations of empirically derived depressive symptom subtypes and gender role orientation, our findings need replication before any conclusions can be drawn.

b) Demographic correlates

Females with low levels of education were shown to be a vulnerable group at risk for depression due to their higher exposure to life-event stressors and chronic problems (van der Waerden et al., 2011). However, in a recent study investigating longitudinally stable subtypes (Lamers et al., 2012b), this risk factor only applied to the severe typical subtype. Our analyses confirmed this finding for females. For males, an association between rural residence and an increased risk of membership in the severe IARS subtype was found. The association between severely depressed subtypes and rural residence is in line with the literature (Carragher et al., 2009; Probst et al., 2006). Rural residents are more likely to experience circumstances, conditions, and behaviors that challenge health, which could increase depression (Probst et al., 2006).

c) Comorbid psychiatric disorders/syndromes

As expected, all severe depression subtypes contained more subjects with affective disorders. In addition, females displayed a higher number of comorbidities, which is coherent with their well-known higher risk of manifesting three or more comorbid disorders. (Kessler et al., 1994). This is explainable with the finding that females endorse a greater overall number of depressive symptoms and more severe forms of depression, which are associated with more comorbidities (Angst et al., 2002a; Kornstein et al., 2000; Rush et al., 2005).

However, eating disorders were linked to the severe atypical subtype in both sexes, which is also consistent with the findings of previous studies (Angst et al., 2006; Kendler et al., 1996). Kendler et al. (1996) attributes this common vulnerability to a familial/genetic aetiology. Moreover, the atypical female subtype showed more alcohol/drug abuse/dependence. These findings are in line with previous results demonstrating that this female-related subtype co-occurs with drug dependence (Matza et al., 2003). In contrast, a previous study found more drug abuse/dependence in melancholia (Leventhal et al., 2008). The conflicting findings may be explained by different samples: normal subjects in the one and clinical subjects in the other study. Our results suggest that the general claim of higher overall comorbidity rates of alcohol/substance abuse/dependence in males suffering from MDD (Carter et al., 1999; Fava et al., 1996) may need to be specified for depressive subtypes.

Psychosis syndromes were more pronounced in the severe subtypes, but did not significantly differ from the moderate subtype. Maj et al. (1990) hypothesized that major depression with mood-congruent psychotic symptoms is not a distinct diagnostic entity, but rather a more severe appearance of depression. We concur with this notion.

Females assigned to the typical subtype were more prone to manifest a comorbid anxiety disorder. Our findings may support the view of Rush (2007), who proposes that the anxious subtype associated with female sex (Clayton et al., 1991; Halbreich and Kahn, 2007) shows more overlap with melancholic than atypical symptom features. Hence, the differing comorbidity profiles between males and females were in line with our initial expectations.

Limitations

In the present study, the following limitations must be acknowledged: First, the study was cross-sectional and no causal conclusions were possible. Second, we did not limit our analyses to subjects meeting the criteria of an MDD. We purposefully chose to remain on the level of depressive symptoms instead of disorders to additionally account for subthreshold symptomatology, as already done in another LCA study (Carragher et al., 2009). Third, we restricted the LCA indicators to depressive symptoms and omitted symptoms from other disorders, such as anxiety disorders or additional somatic syndromes like pain. In consequence, we could not obtain information about the female-related anxious and somatic depression (Clayton et al., 1991; Silverstein, 2002; Silverstein et al., 2006), but were able to examine associations with comorbid disorders. Neither was the potential overlap of the several depressive subtypes considered (Baumeister and Parker, 2012). Fourth, the sample size of the psychomotor retarded subtype was small. Fifth, based on the LCA model fit indices, also the two-class model mainly differing between low- and high-scorers indicated an appropriate model solution within males. From a methodological point of view, this solution was appealing because of its parsimony. From a clinical point of view, this solution could provide additional specification of the high-risk population manifesting severe depressive symptoms, probably in need of an appropriate treatment. However, there were two main arguments against the choice of the two-class model. First, the severity of depression is already assessed by well-established instruments such as the Beck Depression Inventory (BDI) (Beck et al., 1961) or the Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1960) in clinical practice. Therefore the additional benefits of this two-class model were not apparent. Second, the non-specific response of

the heterogeneous MDD to quite differing treatment modalities has led to dissatisfaction with this concept. As Baumeister and Parker (2012) emphasized, delineating depressive subtypes that show differential treatment response should be one of the main objectives of clinical trials. The five-class model included subtypes such as typical and atypical depression, which have been characterized by biological/psychosocial correlates and subtype specific treatment responses in previous studies (Baumeister and Parker, 2012). For these reasons, the choice of the five-class model compared to the two-class model was justified. Obviously, model parsimony is not always the best aim of an analysis.

In conclusion, our study provides a significant contribution to a better understanding of sex-related depression subtypes by deriving homogeneous, symptom-based depressive subtypes in the general population. This forms the basis research for future clinical trials. Males and females revealed similarities and differences in the depressive subtypes. Similarities occurred in the clinical manifestation of the severe atypical, the severe typical, and the moderate subtype. However, apart from the association of the severe atypical subtype with eating disorders, comorbidities and psychosocial characteristics within the same subtype clearly differed between the sexes. Further differences were given by the two male-specific subtypes found in the present study. The main clinical advantages of such homogeneous subtypes are to facilitate communication among mental heath professionals, predict clinical course, and, as mentioned above, identify which treatments are most effective for which subgroup of patients (Baumeister and Parker, 2012; Blashfield and Livesley, 1999; McKay et al., 2004). Regretfully, clinical trials targeting depressive subtypes are still rare, probably due to a lack of interest by pharmaceutical companies (Halbreich and Kahn, 2007). Nevertheless, also our male-related subtypes should need to be delineated from the other depressive subtypes in terms of subtype-specific treatment response in future research. Already now the following clinical implications can be derived: The most frequent male-related subtype seems to be the IARS subtype, which is delimitable through comorbid alcohol/drug abuse/dependence and hypomania/mania. Therefore, this subtype should be recognized in clinical practice. Furthermore, treatment of males manifesting a severe typical depression subtype should consider gender aspects due to the low masculine gender role orientation associated with this subtype. With regard to the DSM classification system, the question arises of how to account for the factor sex in depression. One solution might be to first code the core depressive syndrome and then integrate sex and associated factors as specifiers (Riecher-Rössler, 2010). One could go yet another step further and propose that after validation of overall and sex-related depressive subtypes, these

subtypes may one day even entirely replace the heterogeneous diagnosis of MDD. We believe that this would be a step toward further development of personalized depression treatments.

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Manuscript III: Serum testosterone levels and symptom-based depression subtypes in men

Stephanie Rodgers[a], Martin grosse Holtforth[b,c], Michael P. Hengartner[d], Mario Müller[a], Aleksandra A. Aleksandrowicz[a], Wulf Rössler[a,e,f], Vladeta Ajdacic-Gross[a,*]

[a] Department of Psychiatry, Psychotherapy and Psychosomatics, Zurich University Hospital of Psychiatry, Zurich, Switzerland

[b] Department of Psychology, University of Zurich, Zurich, Switzerland

[c] Department of Psychology, University of Bern, Bern, Switzerland

[d] Department of Applied Psychology, Zurich University of Applied Sciences, Zurich, Switzerland

[e] Collegium Helveticum, University of Zurich and Swiss Federal Institute of Technology, Zurich, Switzerland

[f] University of São Paulo, Institute of Psychiatry, Laboratory of Neuroscience (LIM27), São Paulo, Brazil

[*] Corresponding author

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Abstract

The main objective of this preliminary study was to further clarify the association between T levels and symptom-based depression subtypes male subjects. The analysis included 60 men from the ZInEP epidemiology survey. Gonadal hormones of four depression subtypes (*n*=45, derived from latent class analysis) were compared with healthy controls (*n*=15). Serum T was assayed using an ELISA procedure. Analysis of variance and Fisher's exact tests were performed to examine group differences.

Two of the severe depressive subtypes, i.e. the severe typical subtype and severe irritable/angry rejection sensitive (IARS) subtype, showed significantly higher T levels compared to the controls. The lower T level of the severe atypical subtype was obviously confounded by the high body mass index. Our data indicate that, apart from psychosocial characteristics, neuroendocrinological findings also support an originally symptom-based differentiation of depressive subtypes in men. This hormonal differentiation may indicate distinct, pathophysiological entities to be associated with the depressive subtypes. Further longitudinal research is warranted to disclose the causal processes linking the pathogenesis and neuroendocrinology of depression.

Key words: Testosterone, depression, subtypes, epidemiology, cross-sectional study

Introduction

Apart from its gonadal functions, testosterone (T) has a significant influence on the human brain through various neurobiological processes (1-3). In men, associations between T levels and depressive symptoms have been proposed (3, 4). Such neuroendocrine dysfunctions may play an important role in the pathogenesis of major depression disorder (MDD) (5). In particular, low T levels (hypogonadism) have been associated with depression (4, 6-8), and there is evidence that T secretion is impaired during depressed mood (9, 10). However, this association has not been observed consistently and some studies did not find any relationship between T levels and depression (11, 12). These inconsistent findings could be explained by the heterogeneity of the construct of MDD (13) or difficulties concerning the measurement of salivary T vs. that of serum T (14). Moreover, many findings stem from studies involving exogenous T administration, whereas studies looking at the effects of endogenous T are lacking (15). In sum, there appears to be insufficient evidence to conclude that low T levels is routinely involved in the pathogenesis of MDD in men (15).

However, a growing body of evidence suggests that there may be subpopulations of men vulnerable to depression in whom hypogonadism contributes to depression (16). Some studies showed that low T levels were specifically associated with subthreshold depressive disorders, such as dysthymia or minor depression (15, 17-20). Other studies demonstrated that hypogonadism was related to the specific depressive symptoms of dysphoria, irritability, fatigue, lethargy, decreased libido, and decreased concentration. This symptom cluster has also been conceptualized as ‘irritable male syndrome’, occurring in adult male mammals following withdrawal of T (21).

Meanwhile, some investigations have drawn attention to nonlinear associations between total T levels and depressive symptoms, with increased depression rates at both the lowest and the highest extremes of T levels, (15, 22). Furthermore, exogenous T administration has not only been related to depression but also to hypomania and even mania (23-28). Despite these suggestive findings, to date the associations between elevated endogenous T levels and affective symptoms remain fairly unclear (15).

Apart from the findings with regard to the hypothalamic–pituary–gonadal (HPG) axis, previous studies have investigated the associations between atypical and melancholic (typical) depression and the hypothalamic-pituary-adrenal (HPA) axis, the inflammatory response system and metabolic abnormalities (29, 30). The HPA axis is influenced by gonadal hormones (31). In view of this and the above-summarized findings, we set out to examine the T levels of symptom-based depression subtypes. However, due to the fact that T levels are negatively correlated with the body mass index (BMI) (32), and atypical depression is characterized by a higher BMI (33), it is necessary to consider this confounding variable in the analyses.

This is a preliminary epidemiological study to investigate the differences of serum T levels in symptom-based depression subtypes of men. The following four depressive subtypes were empirically derived in a previous study (34): a severe typical subtype (*n* = 85), a severe atypical subtype (*n* = 65), a male-specific, severe irritable/angry-rejection sensitive (IARS) subtype (*n* = 113), and a moderate subtype (*n* = 94). The severe typical, severe atypical and moderate subtype are in line with previous subtyping approaches and/or the DSM-5 specifiers (33, 35-39). The male-specific IARS subtype showed interesting similarities with Rutz's postulated male depressive syndrome (40, 41). These four depressive subtypes were compared with healthy controls. We expected differing T levels between these depressive subgroups with higher T levels for the hypomania/mania-associated severe IARS subtype and the severe typical subgroup, respectively, and lower T levels for both the moderate subgroup and the severe atypical subgroup. Because of the positive correlation of BMI and atypical depression (33), and the negative correlation of BMI and T, we also suspected that the low T levels would be confounded by the high BMI within the severe atypical depressive subtype.

Methods

Study design and sampling

Data from the epidemiology survey of the Zurich Program for Sustainable Development of Mental Health Services (ZInEP; German: ***Z****ürcher* ***I****mpulsprogramm zur* ***n****achhaltigen* ***E****ntwicklung der* ***P****sychiatrie*) were used. The epidemiology survey was conducted in order to collect comprehensive data about mental health in the general population of adults in the canton of Zurich. The survey was methodologically designed as a cross-sectional sequel to the prospective Zurich cohort study (42), e.g., the instruments and the age structure were parallelized. It consisted of three components: a) a brief telephone screening (*n*=9829), b) a structured face-to-face-interview supplemented by self-report questionnaires (*n*=1500), and c) a laboratory day followed by a longitudinal survey (*n*=227). The survey was carried out between August 2010 and September 2012. In the following, only the laboratory day (c) providing the biological data will be elucidated. For more details with regard to a) and b) see Rodgers et al. (34).

For the laboratory day, a subsample of 227 subjects from the face-to-face sample was selected. The participation rate was 53.8%. All participants performed a set of tests during a day in the sociophysiological laboratory of the Zurich University Hospital of Psychiatry. The participants were interviewed, provided saliva, blood and urine probes, completed computer based tests, and underwent several tests involving electroencephalographic (EEG) and near infrared spectroscopy (NIRS) measurement. All tests were carried out by a biologist and three assistants (psychology students). Furthermore, physicians from the Zurich University Hospital of Psychiatry were involved in the procedure of blood sampling. The gonadal hormones were exclusively derived from the blood probes. However, no gonadal hormone assays were taken from 37 subjects. Of the 190 participants (men: *n*=89; women: *n*=101) with complete hormone data, 137 subjects (72.1%) initially belonged to the stratum of high-scorers, while 53 subjects (27.9%) were low scorers.

The ZInEP epidemiology survey study was approved by the Ethical Committee of the canton of Zurich (KEK) and is in accordance with the latest version of the Declaration of Helsinki. After being extensively informed about study procedure and aims both verbally and in writing, the participants gave their written consent.

Measurements

Depressive symptom subtypes

Depressive symptom subtypes were assessed by a computer-assisted version of the Structured Psychopathological Interview and Rating of the Social Consequences of Psychological Disturbances for Epidemiology (SPIKE) used in the Zurich Study (42, 43). This instrument includes the most common psychopathological syndromes/disorders. The validity and reliability of the SPIKE have been established for the assessment of depression and anxiety (42). For the current study, we made use of depressive subtypes which had previously been extracted by a data-driven technique (latent class analysis, LCA) from the SPIKE data of 373 men manifesting depressive symptoms during the past twelve months (34): a severe irritable/angry-rejection sensitive (IARS) subtype including the largest group of depressed men (30%), a severe typical subtype (22.8%), a severe atypical subtype (17.4%), and a moderate subtype (25.2%). The small psychomotor retarded subtype (4%) was excluded in the current study due to its small class size. The distinction of the severe typical and atypical subtype on the basis of appetite-/weight related symptoms was particularly striking. Members of the severe atypical subtype showed high probabilities of increased appetite and weight gain, whereas the severe typical subtype was characterized by loss of appetite and weight. The severe IARS subtype endorsed high probabilities of symptoms such as irritability/anger, hypersensitivity to critical remarks and low probabilities of weight gain and increased appetite. More detailed information about these depressive subtypes and the entire LCA procedures can be found elsewere (34).

Overall, the T data were available for *n*=89 men. The overlap with the original sample manifesting depressive symptoms (*n*=373) (34), resulted in 46 subjects. A subgroup of 18 controls (defined without use of professional help and low overall GSI-scores) was included. Consequently, the present study was dealing with a sample of 64 subjects.

Psychosocial characteristics

In order to characterize the depression subtypes, sociodemographic variables such as age, education, urbanicity, and marital status were drawn from the face-to-face interview. Axis I diagnoses were computed according to DSM-III-R/IV criteria for the time-period of the past twelve months (44, 45).

Only the diagnosis of neurasthenia was derived from ICD-10 (46). Psychosis syndromes were derived according to the algorithm of Rössler et al. (47), and bipolar disorder in analogy to the BRIDGE study (48). The current smoking status and the GSI was derived from the CATI. Finally, the data concerning the consumption of psychiatric medication was taken from the laboratory day of the longitudinal survey.

Biological measures

Hormones

In order to ensure consistency due to diurnal variation (6) and in accordance with the recommendation of an earlier study (49), the blood sample was drawn in the morning. The exact time frame of the blood sample collection lay between 08:55 AM and 10:34 AM, 01:45 to 03:51 hours after the subject's awakening following an overnight fast. Blood was centrifuged (10 minutes; 3000 rpm) 30 minutes after the sample was taken and stored at –80°C until delivered to the CYTOLAB for biochemical analysis. Total T was derived from serum and measured by Enzyme-Linked Immunosorbent Assay (ELISA) using a kit from IBL International, Hamburg, Germany. Dehydroepiandrosterone-sulfate (DHEA-S), luteinising hormone (LH), estradiol and progesterone were also derived from serum. While DHEA-S, estradiol and progesterone were likewise assayed by ELISA (DHEA-S: IBL International, Hamburg, Germany; estradiol and progesterone: BioCheck, Foster City, USA), LH was measured by Bead-Assay (Millipore, Zug, Switzerland). Sex hormone-binding globulin (SHBG) was derived from Ethylene Diamine Tetraacetic Acid (EDTA) plasma and measured by Enzyme-Linked Immunosorbent Assay (ELISA) using a kit from IBL International, Hamburg, Germany.

Blood pressure and BMI

Blood pressure was measured on the left upper arm in a sitting position at the beginning of the laboratory assessment and 15 minutes later with the Boso Medicus Prestige (Bosch + Sohn GmbH & Co, KG DE). Both systolic and diastolic values were obtained and averaged across the two measurements. Body mass index (BMI) was conventionally calculated, based on mass and height (kg/m^2).

Statistical analysis

All data were analyzed using SPSS version 20 for Macintosh (IBM Corp., Armonk, NY, USA). The criterion for significance was set at $p<0.05$.

First, we identified the T outliers in box plot analyses and extreme value analyses for the 64 subjects. Because the mean differences of small sample sizes are prone to the influence of outliers, we excluded four subjects (moderate subgroup *n*=1; controls *n*=3). Consequently, the sample used for the statistical analyses comprised 60 subjects. Before performing the analysis of variance (ANOVA), Levene's tests were computed in order to examine the homogeneity of variances, and Shapiro-Wilk tests were used to account for the assumption of normally distributed residuals.

Second, unadjusted ANOVA was performed to evaluate the between-group differences on metric dependent variables. The biological/psychological characteristics served as independent variables and T was treated as the dependent variable. Corresponding effect sizes were reported in terms of partial η^2 (0.01 = small, 0.06 = medium, 0.14 = large; 50). In case of significant main effects, Least Significant Differences (LSD) and Games-Howell post-hoc comparisons were computed to explore all possible pairwise subgroup comparisons. Categorical psychosocial/biological characteristics were compared between the subgroups using the Fisher's exact test for categorical variables (two-tailed).

Third, an ANOVA with adjustment for relevant variables was performed and T again served as dependent variable.

Results

Psychosocial characteristics

In Table 1, the psychosocial characteristics of the LCA-based depressive subtypes and the control sample are displayed. No significant differences in demographic correlates were observed between these subsamples. However, groups differed with regard to some comorbid 12-month diagnoses. As expected, the severe depressive subtypes had higher frequencies of MDD diagnosis than the moderate subtype/controls. Hypomania/mania occurred significantly more often in the severe IARS

subtype compared to the severe typical subtype and the control group. The severe atypical subtype revealed a GAD diagnosis more often than the controls. This subtype also showed significantly more psychosis syndromes than the severe IARS subtype and the controls. Finally, in terms of the subjectively rated burden resulting from health problems, all severe depressive subtypes showed significantly higher values compared to the moderate subgroup and controls. Finally, the GSI in the group of controls was lower than in the moderate depressive subtype.

Table 1. Psychosocial characteristics for males belonging to the depressive subtypes derived from latent class analyses (*n*=45) and healthy controls (*n*=15), unadjusted

	Severe IARS[2] No 1 n=14	**Severe atypical No 2 n=12**	**Moderate No 3 n=7**	**Severe typical No 4 n=12**	**Controls No 5 n=15**	
Characteristic [1]						***p*-value F-Test (two-tailed)**
Age						0.900
21	3 (21.4)	1 (8.3)	1 (14.3)	2 (16.7)	2 (13.3)	
23	2 (14.3)	1 (8.3)	3 (42.9)	1 (8.3)	2 (13.3)	
28	3 (21.4)	2 (16.7)	0 (0.0)	1 (8.3)	1 (6.7)	
30	3 (21.4)	3 (25.0)	0 (0.0)	3 (25.0)	5 (33.3)	
35	1 (7.1)	2 (16.7)	2 (28.6)	4 (33.3)	2 (13.3)	
41	2 (14.3)	3 (25.0)	1 (14.3)	1 (8.3)	3 (20.0)	
Education[3] n (%)						0.128
Low	7 (50.0)	6 (50.0)	4 (57.1)	3 (25.0)	2 (14.3)	
High	7 (50.0)	6 (50.0)	3 (42.9)	9 (75.0)	12 (85.7)	
Urbanicity [4] n (%)						0.135
Urban	9 (64.3)	11 (91.7)	7 (100.0)	11 (91.7)	10 (66.7)	
Rural	5 (35.7)	1 (8.3)	0 (0.0)	1 (8.3)	5 (33.3)	
Marital status n (%)						0.685
Unmarried	11 (78.6)	8 (66.7)	7 (100.0)	9 (75.0)	11 (73.3)	
Married	3 (21.4)	3 (25.0)	0 (0.0)	3 (25.0)	4 (26.7)	
Divorced	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Comorbidities[5] (past year) n (%)						
MDD[6]	7 (50.0)	5 (41.7)	0 (0.0)	6 (50.0)	0 (0.0)	<.01 II, IV, VII, VIII, X
Dysthymia[6]	0 (0.0)	2 (16.7)	0 (0.0)	2 (16.7)	0 (0.0)	0.125
Hypomania/Mania[7]	5 (35.7)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	<.05 III, IV
Bipolar disorder[8]	2 (14.3)	2 (16.7)	0 (0.0)	1 (8.3)	0 (0.0)	0.439
Neurasthenia[9, 10]	1 (7.7)	1 (8.3)	0 (0.0)	4 (40.0)	1 (6.7)	0.117
GAD[11]	2 (14.3)	5 (41.7)	0 (0.0)	1 (8.3)	0 (0.0)	<.05 VII
Psychosis syndromes[12]	0 (0.0)	5 (41.7)	0 (0.0)	1 (8.3)	0 (0.0)	<.05 I ,VII
Panic disorder[7]	1 (7.7)	1 (10.0)	0 (0.0)	1 (9.1)	0 (0.0)	0.793
OCD[7]	1 (7.1)	1 (8.3)	1 (14.3)	0 (0.0)	0 (0.0)	0.458
Binge eating[6, 7, 13]	1 (7.1)	4 (33.3)	0 (0.0)	1 (8.3)	1 (6.7)	0.193
Anorexia nervosa[6]	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.750
Suicide attempt	0 (0.0)	1 (11.1)	0 (0.0)	1 (14.3)	0 (0.0)	0.308
Alcohol consumption						0.288
dependence[7]	5 (35.7)	3 (25.0)	0 (0.0)	3 (25.0)	1 (6.7)	
subthreshold	4 (28.6)	3 (25.0)	3 (42.9)	3 (25.0)	10 (66.7)	
Other	5 (35.7)	6 (50.0)	4 (57.1)	6 (50.0)	4 (26.7)	
Current smoking	7 (50.0)	3 (25.0)	2 (28.6)	5 (41.7)	5 (33.3)	0.716
Psychopharma-ceuticals n (%) [14]	2 (16.7)	4 (36.4)	0 (0.0)	2 (33.3)	0 (0.0)	0.680
Antidepressant	1	4	0	1	0	
Mood stabilizer	0	1	0	1	0	
Sedative, hypnotic, anxiolytic	0	1	0	0	0	
Neuroleptics	0	1	0	0	0	
Other	1	1	0	0	0	
						One-way ANOVA/*post hoc* tests [16]
Subjective impairment (mean+- SE) [15]						
GSI	2.12 (+- 0.09)	2.32 (+- 0.18)	1.67 (+- 0.14)	2.19 (+- 0.11)	1.31 (+- 0.07)	<0.001 II, IV, V, VII, VIII, X, IX

Abbreviations: MDD, major depressive disorder; DYST, dysthymia; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder

[1] The discrepancy between the total number of persons and the number of persons in the following rows result from missing items;
[2] Severe irritable/angry-rejection sensitive; [3] Although the Swiss educational degrees do not entirely correspond with the school system of Anglo-American areas or other countries, the educational degrees were comparatively grouped into the two following categories: low=less than high school diploma; high= high school diploma or higher; [4] Urban: Zurich, Winterthur; rural: remaining municipalities of the canton of Zurich; [5] 12-month prevalence; [6] DSM-III-R; [7] DSM-IV; [8] Def. BRIDGE study (Angst et al., 2011); [9] ICD-10; [10] 3 month criteria;
[11] DSM-III; [12] Disorders of form of thought, derealization, depersonalization, delusion, disorder of ego-boundary, hallucinations, paranoia syndrome; [13] Including binge eating symptoms; [14] Consumption of psychopharmaceuticals during the past six month; [15] Global Severity Index (GSI) of the SCL-27 (Hardt et al., 2004); [16] Post hoc tests: Least significant difference (LSD); [I] No 1 significantly differs from No 2; [II] No 1 significantly differs from No 3; [III] No 1 significantly differs from No 4; [IV] No 1 significantly differs from No 5; [V] No 2 significantly differs from No 3; [VI] No 2 significantly differs from No 4; [VII] No 2 significantly differs from No 5; [VIII] No 3 significantly differs from No 4; [IX] No 3 significantly differs from No 5; [X] No 4 significantly differs from No 5.

Biological characteristics

The unadjusted biological characteristics of the five subsamples are summarized in Table 2. The severe atypical subtype differed significantly from the severe IARS subtype and the controls with regard to lower T levels. Moreover, men manifesting atypical depressive symptom configurations were significantly more prone to a higher BMI than all other subgroups. In an exploratory extension of the analyses, the biological factors were categorized in order to validate these results in terms of medically relevant cut-offs (data not tabulated): hypogonadism, which was defined as <2.3 ng/mL (52), only occurred in *n*=2 (16.7%) men belonging to the severe atypical subtype and the overall group differences could only be expressed as trend level associations (χ^2=8.276, *df*=4, *p*=0.086). The categorized BMI (normal weight: BMI 18.50-25.00; overweight: BMI 25.01-30.00; obesity: >=30.01) showed significant overall differences (χ^2=21.603, *df*=8, *p*<0.05) with differing frequencies between the severe atypical subtype (normal weight: *n*=4 (36.4%); overweight: *n*=3 (27.3%); obesity: *n*=4 (36.4%)) and the subgroups severe IARS (normal weight: *n*=10 (71.4%); overweight: *n*=4 (28.6%); obesity: *n*=0 (0.0%)), moderate (normal weight: *n*=5 (71.4%); overweight: *n*=2 (28.6%); obesity: *n*=0 (0.0%)), and controls (normal weight: *n*=11 (73.3%); overweight: *n*=4 (26.7%); obesity: *n*=0 (0.0%)), respectively. The categorized blood pressure revealed no single cases of hypotension (defined as <90/60mm/Hg). In contrast, hypertension (defined as >140/90mm/Hg) occurred most frequently in the severe IARS subtype (*n*=5; 35.7%) and the severe typical subtype (*n*=5; 41.7%), respectively. Controls more often had normal blood pressure. The overall differences remained on a trend level (χ^2=9.788, *df*=4, *p*=0.051).

Table 2. Biological characteristics of males belonging to the depressive subtypes derived from latent class analyses (*n*=45) and healthy controls (*n*=15), unadjusted

Biological characteristics	Severe IARS [1] (*n*=14) No 1	Severe atypical (*n*=12) No 2	Moderate (*n*=7) No 3	Severe typical (*n*=12) Subgroup No 4	Controls (*n*=15) Subgroup No 5		*p*-value
	Mean (s.e.)	Mean (s.e.)	Mean (s.e.)	Mean (s.e.)	Mean (s.e.)	Eta (η^2)	One-way ANOVA/*post hoc* tests [2]
Testosterone (ng ml)	5.22 (0.41)	3.92 (0.39)	4.78 (0.30)	5.33 (0.32)	4.35 (0.26)	0.18	$p < 0.05$ [I, VI]
SHBG (nmol/L)	41.08 (4.34)	25.67 (5.22)	49.00 (6.39)	42.58 (4.52)	39.17 (6.39)	0.19	$p = .061$
DHEA-S (ug/mL)	2.54 (0.21)	2.25 (0.23)	2.59 (0.30)	2.28 (0.23)	2.15 (0.21)	0.05	$p = .629$
Estradiol (ng/mL)	26.69 (2.15)	29.48 (2.32)	25.13 (3.03)	25.37 (2.32)	26.07 (2.07)	0.04	$p = .712$
Progesterone (ng/mL)	1.19 (0.14)	0.86 (0.16)	0.94 (0.20)	0.83 (0.16)	0.95 (0.14)	0.06	$p = .455$
Luteinising hormone (LH) (mlU/ml)	2.96 (0.62)	2.70 (0.78)	4.54 (0.95)	3.14 (0.67)	2.39 (0.95)	0.07	$p = .541$
BMI	24.31 (0.91)	29.44 (1.03)	22.97 (1.29)	23.29 (0.98)	23.05 (0.88)	0.35	$p < 0.001$ [V, VI, VII]
Systolic BP (mm Hg)	136.29 (3.47)	132.18 (3.92)	127.00 (4.91)	132.46 (3.75)	129.07 (3.36)	0.06	$p = .511$
Diastolic BP (mm Hg)	86.79 (2.90)	88.36 (3.27)	80.64 (4.10)	85.88 (3.13)	82.23 (2.80)	0.06	$p = .467$

[1] Severe irritable/angry-rejection sensitive; [2] Post hoc tests: Least Significant Difference (LSD) (homogeneous variances), Games-Howell (non-homogeneous variances); [I] No 1 significantly differs from No 2; [II] No 1 significantly differs from No 3; [III] No 1 significantly differs from No 4; [IV] No 1 significantly differs from No 5; [V] No 2 significantly differs from No 3; [VI] No 2 significantly differs from No 4; [VII] No 2 significantly differs from No 5; [VIII] No 3 significantly differs from No 4; [IX] No 3 significantly differs from No 5; [X] No 4 significantly differs from No 5.

The results after adjusting for BMI, hypomania/mania, psychosis syndromes, and GAD revealed a different picture. The overall group comparison remained significant (F=2.65; df=4; p<0.05). The differences had an effect size of η^2= 0.18, representing a large effect. Pairwise comparisons (Least Significant Differences) showed that the severe IARS subtype and the severe typical subtype remained characterized by significantly higher T values in comparison with the controls (p<0.05). However, no significant differences were found for the severe atypical subtype after adjustment. For a visual comparison, the unadjusted and adjusted serum T levels separated into the four depressive subtypes and controls are plotted in Fig. 1.

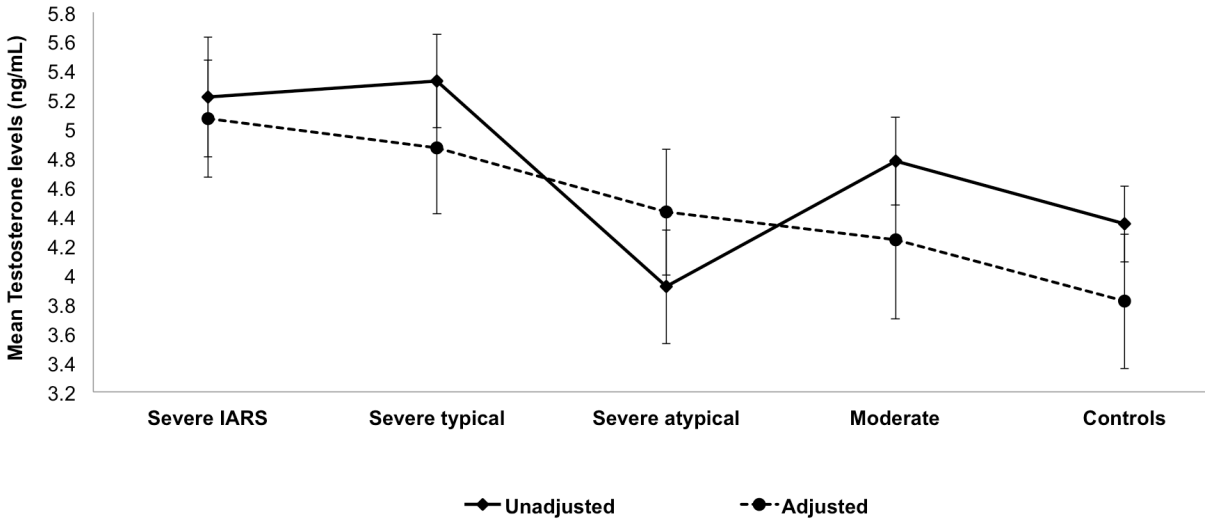

Fig. 1. Comparison of mean (+/- s.e.) serum testosterone levels between the depressive subtypes and healthy controls before and after adjustment for body mass index (BMI), hypomania/mania, psychosis syndromes, and generalized anxiety disorder (GAD).

Additional exploratory analysis excluding the control group revealed that the severe atypical subtype remained characterized by significantly lower T levels compared to the severe IARS subtype and the severe typical subtype, but this difference disappeared when BMI was controlled for (data not shown).

The results of the current study provided evidence that the empirically derived symptom-based depression subtypes are discriminable by differing serum T levels in men.

Discussion

This is the first study examining differences of serum T levels in four empirically derived symptom-based depression subtypes and a healthy control group in a Swiss community subsample of male adults. We found significantly higher T levels within the severe IARS subtype and the severe typical subtype compared to the controls. The low T levels of the severe atypical depressed subgroup appearing in bivariate analyses were obviously confounded by the high BMI of this subgroup. First, our results support the notion that the inconsistent evidence from previous studies with respect to T levels and MDD may have resulted from the heterogeneity of this diagnosis, while the investigation of more homogeneous symptom-based subtypes provides a more differentiating picture. Second,

the current analyses demonstrated that two of the recently found depressive subtypes in men (34) cannot only be characterized by psychosocial characteristics, such as comorbid disorders, but also by the gonadal hormone T.

The significantly high T levels in the hypomania/mania-related severe IARS depression subtype and the severe typical subtype were in line with our prior expectations, which were based on the available literature with regard to exogenous T administration, demonstrating that high T doses resulted in both depression and hypomania/mania (24-28). Hence, the present study found evidence for analogical findings with respect to endogenous T levels. A quite recent community study on a sample of men showed a positive correlation between endogenous evening saliva T and overall depression scores (53, 54). Moreover, Sigurdsson et al. (53) revealed a positive correlation between evening T levels and evening cortisol (HPA axis). This relation is explainable by the effect of cortisol modifying the gonadotropin-releasing hormone (GnRH) from the hypothalamus, by influencing the luteinizing hormone (LH) from the pituary or by alterations of stimulating effect of gonadotropins or gonads (53, 55). Taking into account that melancholic (typical) depression has been associated with HPA axis hyperactivity (4, 29), the high T levels of the severe typical subtype found in the current study are plausible. Despite its distinct symptom-profile and specific comorbid disorders/syndromes, the severe IARS subtype revealed a biological similarity to the severe typical depression subtype. This similarity on a biological level was not only found with regard to T levels but also by the occurrence of hypertension (which is a risk factor for cardiovascular diseases (CVD)) in both subtypes, albeit only on a trend level. Depression and CVD are related (56). The exact pathophysiological mechanisms and interactions of these biological markers, particularly between the HPA- and HPG axis, require further longitudinal investigation.

In contrast to the biological similarities between the severe IARS subtype and the severe typical subtype, the third severe subtype with the atypical profile was presented as diametrically opposed. Studies have demonstrated the biological characteristic of this subtype by its down regulated HPA axis resulting in hypocortisolemia (4). In line with previous findings (29, 33), there was a striking association between a higher BMI and membership in the severe atypical subtype. Furthermore, we found lower T levels in this severe depression subtype, at least bivariately. But as expected, these lower T levels were confounded by the BMI. The effect sizes of these two biological markers allowed for more clarification. Although the partial η^{2}'s were large for both variables, the effect size of the BMI was more than twice as large as that of T. Whereas at first glance the 'irritable male syndrome',

a behavioral state following withdrawal of T in adult male mammals (21), resembled the severe atypical subtype within human adults, the BMI and not the low T levels was the relevant biological marker of this subtype in the present study.

Contrary to our initial expectations, low T levels were not significantly linked to the moderate subtype. This is discrepant with other studies showing a relationship between low T levels and subthreshold depressive disorders (15, 17, 20). One epidemiological study reported that lower T levels are only associated with subthreshold symptoms of anxiety and depression (19). Anxiety symptoms were not included as LCA indicators when deriving the depressive subtypes (34). The inconsistent results could also stem from the younger age range in our sample, the divergent conceptualization of the subthreshold depressive categories (DSM-categories of dysthymia or minor depression vs. data-derived moderate subtype in the current study), and/or the missing control group in some studies. However, as Jäger et al. (57) emphasized, the comparison of studies examining this issue is difficult because there is no international consensus on the definition of a standardized normal range of hypogonadism. Although not achieving common significance levels, the high SHBG levels and LH levels of the moderate subtype were striking. Future studies should focus on this issue.

The parabolic model displaying a curvilinear relationship between T and depression (13, 15, 22) could only be replicated without adjustment for BMI in the current data. In the unadjusted analyses, the mean T levels of all three severe subtypes lay at both the highest and lowest extremes of the distribution (severe typical and severe IARS subtype at the highest end; severe atypical subtype at the lowest end). However, with adjustment for BMI, the moderate subtype showed the lowest T levels, and the control group exhibited even lower levels and differed significantly from the two high T-level groups.

Apart from T, no other hormones achieved a common statistical significance level. Only a trend level association was found for SHBG, which is not surprising taking into account that it is correlated with T (32).

The following limitations should be noted. First, the sample sizes of the examined subsamples were small. We performed outlier analyses, but nevertheless our findings could be the result of influential observations/hormonal fluctuations. Therefore, replications of our findings with representative,

large samples are necessary. Furthermore, only very strong effects achieve common significance levels with small sample sizes. We accommodated this limitation by additional computation of effect sizes. Second, we cannot draw causal conclusions from our data due to the cross-sectional design, although there is some evidence suggesting that the differing T levels are a consequence rather than a cause of affective symptoms (58). Future studies are required to replicate our findings, to longitudinally analyze causal processes (particularly with regard to the interaction between HPG- and HPA axis), and to assess a broader age range in order to consider the possibility of age-specific features (59-61). Third, the participants of the laboratory day were selected as convenience sample. Consequently, a certain selection bias and a restricted external validity cannot be completely excluded. Fourth, we draw analogies between the effects of exogenous high dose T with endogenous serum T values although we can not ensure there is a direct correlation between these biological markers. Fifth, as shown in the literature (62), weight gain is commonly associated with psychotropic drugs. Therefore, this confounding variable directly affecting BMI, and thus indirectly the T levels, should be examined in more detail, e.g., with path models. Sixth, the calculation of free testosterone using total T and SHGB (63) could be added in future research.

Despite these limitations and its preliminary nature, this community study demonstrated for the first time higher serum T levels of two empirically derived severe symptom-based depression subtypes compared to healthy controls in men. These depressive subtypes have previously been differentiated by psychosocial characteristics (34) and are an attempt to deal with the heterogeneity of the MDD diagnosis. If the current biological findings would be replicated in larger samples, the differentiation of depressive subtypes by biopsychosocial features may indicate distinctive pathophysiological entities and could ameliorate specificity of depression diagnoses and treatments.

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3. Discussion

In the final section of the doctoral thesis the most important findings from the three conducted studies will be discussed in a broader framework, attempting to answer the four major questions first mentioned in the introduction.

3.1 Replication of symptom-based subtypes in two independent samples

- *Can the empirically derived symptom-based depression subtypes be replicated in different samples, and secondly, can they be replicated both cross-sectionally and longitudinally?*

Replication studies are the key strategy to assess the external validity of previous research findings (Fahs, Morgan, & Kalman, 2003; Ferguson, 2004; Hayes, 1998). First described by Campbell and Stanley (1963), external validity describes whether the detected causal relationship is maintained over variations in person, settings, time or treatment variables, and thus can be generalized (Ferguson, 2004).

In the first study (manuscript I) I set out to examine the influence of sex on stability and transition patterns of empirically derived subtypes over the time span of 20 years. Latent transition analysis (LTA), which is the longitudinal extension of latent class analysis (LCA), was performed. Additionally, the role of sex on stability and change of depression subtypes was considered by including sex as a model covariate. Three symptom-based subtypes were found: a severe typical subtype, a severe atypical subtype and a moderate subtype. Both the severe atypical and the moderate subtype showed high long-term stability which even increased over time. In contrast, the severe typical subtype revealed a remarkably lower stability. The reliability of the results was comparable to the stability values of other studies applying other methodological approaches (for more details and references, see manuscript I). Moreover, it could be demonstrated that particularly transitions from the severe typical subtype to the severe atypical subtype (and vice versa) and to the moderate subtypes were prominent. In this context, this study was the first to show striking sex-specific longitudinal patterns, which will be summarized and discussed in chapter 3.2.

On the basis of these results I was curious to empirically derive depression subtypes in a further, cross-sectional dataset, the ZInEP survey (manuscript II). This survey was methodologically linked to

the Zurich Study, however, the sample was composed of other subjects. My expectations were to replicate the severe typical and severe atypical subtype found in manuscript I. The cross-sectional version of mixture modeling, LCA, was applied and the analysis was separated by sex as this factor was largely neglected in previous studies using this approach. In line with the a priori expectations, a severe typical subtype, and a severe atypical subtype were detected. Moreover, the moderate subtype for both males and females could even be replicated. The existence of the two subtypes typical depression and atypical depression was consistent with earlier mixture modeling subtyping studies (Kendler et al., 1996; Lamers, Burstein, et al., 2012; Lamers et al., 2010; Lamers, Rhebergen, et al., 2012; Sullivan, Kessler, & Kendler, 1998; Sullivan, Prescott, & Kendler, 2002), and the specifiers available in DSM-5 (APA, 2013). The moderate depressive subtype underlined the findings of previous studies (Lamers et al., 2010; Lamers, Rhebergen, et al., 2012), while some studies on larger sample sizes were even able to differentiate mild/moderate atypical and/or mild/moderate typical depression subtypes (Kendler et al., 1996; Lamers, Burstein, et al., 2012; Sullivan et al., 1998). A distinction in terms of severity is also suggested by DSM-5 (APA, 2013).

The descriptive validity of the typical (melancholic) subtype was previously questioned (Melartin et al., 2004). Yet, the twofold efforts in empirically finding symptom-based subtypes (manuscript I/II) demonstrated that a typical subtype was clearly derivable and phenomenologically replicable, consequently supporting the validity of this psychopathological construct. Although, if temporal stability constitutes an aspect of the usefulness of psychopathological classifications (Kendell, 1974), this first conclusion needs to be rethought, because the stability coefficients for the severe typical subtype were markedly lower than for the other subtypes described in manuscript I. However, the view on stability was extended by the investigation of transition patterns revealing pronounced transitions from the severe typical to the severe atypical subtype and vice versa (manuscript I), showing that not only stability but also longitudinal transition patterns might be considered as promising features of symptom-based depression subtypes, which could be useful for diagnoses in the future. The recently postulated ‘switch-hypothesis’ (O'Keane, Frodl, & Dinan, 2012) suggesting a biological link between changing profiles of typical (melancholic) and atypical subtypes (for more detailed information see chapter 3.3) supported the biological relevance of transition movements too. Consequently, the current data provided evidence that the typical symptom conglomerate represents a valid and useful symptom-based subtype. However, an issue that still requires further investigation is the conceptual overlap between the diagnostic criteria of MDD and the specifier melancholic (typical) depression (Parker, 2009).

Despite the obvious validity of the atypical depressive subtype, also confirmed by the present studies (manuscript I/II), there is still no consensus on its most eligible diagnostic criteria to date, and among the five specifiers the validity of mood reactivity and rejection sensitivity has been doubted most (Angst, Gamma, Sellaro, Zhang, & Merikangas, 2002; Benazzi, 2002b; Parker et al., 2002; Thase, Carpenter, Kupfer, & Frank, 1991). In fact, mood reactivity did not well distinguish between the atypical and typical subgroups in the present analyses for both sexes (manuscript II). In contrast, the reversed neurovegetative symptoms (weight gain and increased appetite) provided the best distinguishing feature for the atypical class (manuscript I/II). These criteria have consistently been confirmed as atypical features in several studies (Benazzi, 2002a; Kendler et al., 1996; Sullivan et al., 2002). Hence, the findings underscore the concerns raised regarding the validity of mood reactivity as the main and hierarchical criterion of atypical depression and, as already claimed by Thase (2009), a revision of the criteria of atypical depression seems appropriate. Unfortunately, the revision of the criteria of atypical depression has been omitted in the recently published DSM-5 (APA, 2013), notwithstanding that new specifiers (e.g., anxious distress, with mixed features) were added to the MDD diagnosis.

The initially not hypothesized moderate subtype was distinguishable from the severe subtypes by its lower overall probability for depressive symptoms. Although its symptom profile had a certain resemblance to the typical subtype, this similarity was not fully replicated over the two studies (manuscript I/II). Subjects belonging to the moderate subtype were characterized by a lower subjective distress/burden compared to members of the severe subtypes and a higher frequency of defined low scorers (cut-off criterion: 75th percentile of the GSI of the SCL-27 (Hardt, Egle, Kappis, Hessel, & Brahler, 2004), page 15 and 16, manuscript II). These findings indicate different severity levels of depressive states, as proposed by the unitarian model of depression, conceptualizing this disorder as a single condition only varying by its levels of severity (Baumeister & Parker, 2012; Parker, 2000). However, as we shall see in chapter 3.5, the unitarian model is not sufficient to explain all aspects of depressive phenomenology under consideration of symptom-based depression subtypes.

Due to reasons of model parsimony no psychotic symptoms were included as indicators. As a consequence, neither of the two studies (manuscript I/II) extracted a psychotic depressive subtype, although it is classified as a further MDD specifier in DSM-5 (APA, 2013). Nevertheless, the data supported the notion that psychotic depression may rather be a more severe appearance of

depression than a distinct symptom cluster due to the fact that psychosis syndromes were more pronounced in the severe subtypes versus the moderate subtypes (manuscript I/II) (although multivariately only significant in manuscript I).

Based on these summarized finding the validity of the typical-, the atypical depression subtype, and the moderate subtype could be confirmed by the successful replication in two independent samples applying mixture modeling to both cross-sectional data and longitudinal data (manuscript I/II). The potential and benefit of longitudinal data was demonstrated anew by the fascinating finding of the subgroup of depressive individuals switching between typical and atypical states.

3.2 Sex-related and sex-specific symptom-based subtypes

- *Which kind of sex-related and sex-specific symptom-based depression subtypes can be empirically derived? How do they correspond with the existing psychopathological constructs and theories?*

The consistently reported higher MDD prevalence of females (Alonso et al., 2004; Kessler, 2003) has been attributed to the higher occurrence of certain female-related symptom-based depression subtypes such as atypical depression (Angst et al., 2002; Benazzi, 1999; Halbreich & Kahn, 2007; Posternak & Zimmerman, 2001, 2002). The striking association of this severe depressive subtype with female sex could be confirmed in manuscripts I/II. Unexpectedly, male sex was associated with both the longitudinally stable and cross-sectionally derived severe typical subtype (manuscript I/II). An intensive literature research revealed an increasing body of literature supporting the view that the typical (melancholic) subtype may be a male-related depression phenotype (Angst, Gamma, Benazzi, Ajdacic, & Rossler, 2007; Hildebrandt, Stage, & Kragh-Soerensen, 2003; Xiang et al., 2012). Beyond this male-related subtype, the best fitting LCA solution in manuscript II derived two further male-specific subtypes comprising the largest and the smallest group of males, respectively: a severe irritable/angry-rejection sensitive (IARS) subtype, distinguishable from the atypical subtype by the lacking atypical criteria such as weight gain and increased appetite, and a psychomotor retarded subtype. The detection of these two depression subtypes confirmed the initial expectations regarding the explorative potential of the mixture modeling method in detecting sex-related depression subtypes. Probably, the larger sample size of manuscript II compared to manuscript I

enhanced the statistical power in so doing. However, the interpretability and theoretical appropriateness of a mixture modeling solution should always be considered (Muthén, 2004). At first glance, the severe IARS subtype resembled Rutz's male depressive syndrome (Rutz, 1999; Rutz, von Knorring, Pihlgren, Rihmer, & Walinder, 1995), but there were also features lacking, e.g., no association with antisocial symptoms/disorder, not definitely confirming this overlap. Furthermore, the Gotland Scale that aims at assessing the male depressive syndrome, neither distinguished between males and females nor between the severe sex-specific/-related depressive subtypes in the present data. This finding is in line with two previous studies demonstrating that the Gotland Scale captured male depression in both sexes (Innamorati et al., 2011; Möller Leimkühler & Yucel, 2010). Males belonging to the small psychomotor retarded subtype exhibited a high probability of psychomotor retardation, insomnia, concentration and memory problems, however, no loss of self-confidence/guilt. The association of psychomotor retardation with male depression, and moreover, the discriminative power of psychomotor activity in differentiating depressive subgroups in males underlined the results of two other studies (Alexandrino-Silva et al., 2013; Sobin & Sackeim, 1997).

For the first time, interesting sex-related features of depressive subtypes with regard to their long-term stability and change could be demonstrated (manuscript I), which was in line with the a priori expectations. Males displayed high stability within the depression subtypes over time. In other words, once in a depressive subtype, males remained in it, at least over the examined period of 20 years. Under consideration of the high suicide rates of males (Hausmann, Rutz, & Benke, 2008), this chronicity of depression subtypes needs specific clinical attention. In contrast, females revealed more transitions between the subtypes, and transitions between the severe typical and the severe atypical subtype were particularly prominent. A possible biological explanation for the latter occurrence will be provided in the following chapter 3.3.

Altogether, the following depression subtypes were empirically derived: a female-related severe atypical depressive subtype (manuscript I/II), a male-related severe typical depressive subtype (manuscript I/II), and two male-specific depression subtypes: a severe IARS subtype, partly resembling Rutz's male depressive syndrome (Rutz, 1999; Rutz et al., 1995), and a psychomotor retarded subtype (manuscript II). The male-specific depressive subtypes are novel and therefore need replication in future studies. Finally, the longitudinal study design provided the new finding that males show a higher stability within the depressive subtypes, while females display more transitions between the depression subtypes.

Albeit the high female to male sex ratio of MDD is well attributable to female-related subtypes such as atypical depression, the exact etiopathogenetic mechanisms leading to these sex-associated effects still remain unclear. However, considering that the human brain is an impressive product of evolution, it is likely that natural selection has not only shaped its internal biology, but indirectly also the main pathways of our mental processes and overall behaviors (Mataix-Cols, Rosario-Campos, & Leckman, 2005). For example, depressive mood can occur as reaction to infection resulting in social withdrawal and in this way supporting the recovery process of the individual and, moreover, security for the population (Wittman, 2014). I think however that within mental disorders these biologic-evolutionary developed advantageous mental pathways/networks derail in their severity and course. These mental processes rely both on vulnerability factors (e.g., female sex, family burden of depression) and triggers (e.g., critical life events), which can be sex-specific (e.g., coping-style of rumination, sociocultural with related vulnerability to adverse life events, monthly cycling, critical role of microglia and astrocytes) or not (e.g., influenza A virus) (Grigoriadis & Robinson, 2007; Halbreich & Kahn, 2007; Piccinelli & Wilkinson, 2000; Schwarz & Bilbo, 2012).

3.3 Biopsychosocial characteristics of the sex-related, sex-specific and non-sex-specific symptom-based subtypes

- *Are the empirically derived symptom-based depression subtypes characterized by biopsychosocial correlates?*

In the following subsections, the most important converging findings from manuscript I, II and III regarding biopsychosocial characteristics of the empirically derived depressive subtypes will be briefly outlined and discussed. The characterization of the psychomotor retarded was omitted due to its small sample size making multivariate analyses not feasible.

3.3.1 Severe typical subtype

The analyses of the sociodemographic characterization of the severe typical depression subtype yielded only few informative results (manuscript I/II). Unemployment was a critical life event associated with the severe typical class in manuscript I, while low education was linked to the severe

typical subtype in females in manuscript II. With regard to gender role orientation, interesting results were found within typical depressed males. Males belonging to the severe typical subtype exhibited a significantly less expressed masculine gender role compared to the moderate subtype (manuscript II). This study was the first differentiating that the previously found protective effect of masculine gender role orientation against overall depression (Helgeson, 2005) may have resulted from the two symptom-based depressive subtypes moderate versus severe typical subtype. However, this being the first study investigating associations between data-driven depression subtypes and gender role orientation, the findings require replication.

Additionally, comorbid disorders of the severe typical depressive subtype were examined. Females belonging to the typical subtype showed more anxiety disorders (manuscript II). This may indicate that the female-related anxious subtype (Clayton et al., 1991; Halbreich & Kahn, 2007) overlaps more strongly with melancholic (typical) symptoms than with atypical features (Rush, 2007). My a priori expectation of differing comorbidity profiles between males and females was therefore confirmed. As already mentioned in chapter 3.1, the stable severe typical subtype was associated with psychosis syndromes in males and females (manuscript I), possibly indicating a higher depression severity of this subtype.

With regard to biological features, gonadal hormones within the subsample of depressive males were analyzed (manuscript III). Despite recent studies demonstrated that particularly low testosterone levels were associated with more severe affective symptoms, an increasing body of evidence has suggested that also high testosterone levels may be linked to pronounced depressive phenomenology (e.g., Booth, Johnson, & Granger, 1999; Johnson, Nachtigall, & Stern, 2013). For the first time, these associations were examined under consideration of symptom-based depression subtypes. In line with the expectations, males belonging to the severe typical subtype showed significantly higher serum testosterone levels compared to the controls. Melancholic (typical) depression has been associated with HPA axis (cortisol)-hyperactivity (Baumeister & Parker, 2012; Lamers et al., 2013). Cortisol can influence the hypothalamic-pituitary-gonadal (HPG) axis (testosterone) by the gonadotropin-releasing hormone (GnRH) from the hypothalamus, by influencing the luteinizing hormone (LH) from the pituitary, or by alterations of stimulating effect of gonadotropins or gonads (Sigurdsson, Palsson, Aevarsson, Olafsdottir, & Johannsson, 2014), Moreover, a recent study revealed a positive correlation between evening saliva testosterone and evening cortisol (Rivier & Rivest, 1991; Sigurdsson et al., 2014). Considering these previous findings,

the present results distinguishing symptom-based depression subtypes appear plausible.

To summarize: whereas a meta-review demonstrated that previous findings regarding psychosocial correlates of typical (aka melancholic) depression have led to inconclusive evidence (e.g., Booth et al., 1999; Johnson et al., 2013), this was true for sociodemographic features in the current studies (apart from the powerful factor sex). In addition to its association with male sex, the severe typical subtype was characterized by the biological marker of higher testosterone levels in males, confirming the greater relevance of biologic causes compared to psychosocial causes in melancholic depression (Parker, 2009). Somewhat confusing was the coexistent finding of high testosterone levels and low masculinity in this subtype, despite earlier studies finding positive correlations between testosterone levels and masculinity (Baucom, Besch, & Callahan, 1985). The small sample size with available testosterone data limits a final conclusion. However, a recent review concluded that high testosterone does not map onto masculinity or its manifestations (van Anders, 2013), which would mean that gonadal hormones do not dictate social gender role orientation.

3.3.2 Severe atypical subtype

As already demonstrated for the severe typical subtype, the severe atypical subtype could also not be consistently characterized by sociodemographic features other than sex. In contrast, the comorbidity patterns of the severe atypical depression subtype indicated a highly consistent picture with regard to comorbid eating disorders such as bulimia and binge eating in both males and females (manuscript I/II). The consistently replicated co-occurrence of atypical depression and eating disorders was attributed to a familial/ genetic etiology (Baumeister & Parker, 2012; Kendler et al., 1996). The higher BMI of subjects belonging to the severe atypical subtype (manuscript III) was striking and in line with the literature (Kendler et al., 1996). In contrast, the association of the severe atypical subtype with substance use in females (manuscript II) remained somewhat indistinct. On the one hand some evidence confirmed that female-related atypical depression co-occurs with drug dependence (Matza, Revicki, Davidson, & Stewart, 2003), on the other hand some findings indicated that drug abuse/dependence is associated with melancholic (typical) depression (Leventhal, Francione Witt, & Zimmerman, 2008). These conflicting results may stem from the different sample composition of the studies: non-clinical subjects (Matza et al., 2003) versus patients (Leventhal et al., 2008). Congruent with the stable severe typical subtype, also the stable severe

atypical subtype was associated with psychosis syndromes again indicating a higher illness severity (manuscript I).

Motivated by the evidence with regard to the biological component of the atypical depressive phenomenology and its comorbid features, I examined the testosterone levels of the severe atypical subtype in the subsample of males (manuscript III). At first sight, this depressive subtype actually disclosed a delimitable testosterone profile with significantly lower testosterone levels compared to the controls. However, the analyses were repeated multivariately, controlling for BMI due to the following facts: while BMI and atypical depression are positively correlated (Kendler et al., 1996), BMI and testosterone and are negatively associated (Zitzmann & Nieschlag, 2001). Based on this knowledge, lower testosterone levels for depressive subgroups associated with high BMI were initially expected. However, the testosterone levels of the severe atypical subtype were no longer significant at second sight – the variance between the severe atypical subtype and low testosterone had been confounded by the BMI, and moreover, was better explained by the latter.

To conclude, the severe atypical subtype was not only distinguishable by its distinct symptom-profile and its association with female sex, but also by its consistent comorbidity with eating disorders. Furthermore I conclude for the subsample of males that the examination of atypical depression and testosterone levels without consideration of BMI is misleading.

3.3.3 'Switchers' between the typical and atypical subtype

Levitan and Colleagues (1997) found a group of depressed subjects fluctuating between typical and atypical episodes. This subgroup manifested high rates of comorbid disorders. The authors proposed that in the previous examination of atypical depression these fluctuating persons (in the following termed as 'switchers') have led to overestimated prevalence of comorbidities, e.g., bipolar disorders. When, in contrast, only longitudinally stable depression subtypes were investigated, numerous comorbidities disappeared and the major comorbid disorder of atypical depression remained eating disorders (Levitan et al., 1997). The restricted comorbidity patterns of the stable, long-term subtypes (manuscript I) compared to the cross-sectional comorbidity patterns (manuscript II) confirmed this assumption. Consequently, the comorbidities described in manuscript II may have

been overestimated due to the lacking possibility to cross-sectionally extract the subgroup of long-term-'switchers'.

Interestingly, a recent study has hypothesized a biological link between changing depressive symptom profiles of typical (melancholic) and atypical subtypes (O'Keane et al., 2012). This depression subgroup refers to the 'switchers' described above. In their 'switch hypothesis', O'Keane et al. (2012) associated this subgroup with specific dysregulations of the HPA axis. The HPA axis is also influenced by ovarian hormones (Young & Korszun, 2010), and the cycle-dependent vulnerability for affective symptoms has been demonstrated by prospective surveys (Kuehner, 2003; Ramcharan, Love, Fick, & Goldfien, 1992). Hence, I speculate that the frequent transitions between the depressive subtypes found in females (manuscript I) may be attributed to hormonal fluctuations of the perimenstrual phase.

In sum, the important issue of 'switchers', i.e., subjects switching between the symptom-based depression subtypes, has been underestimated in depression research up to date. Exclusively the longitudinal data provided evidence for this subgroup of depressives. Future prospective longitudinal research with large sample sizes is required to examine this topic in more detail and to investigate if additional switching processes between further subtypes exist.

3.3.4 Severe irritable/angry-rejection sensitive subtype

The male-specific, severe IARS subtype found in manuscript II was associated with rural residence. This is in accordance with previous findings highlighting rural residence as risk factor for severe depression subtypes (Carragher, Adamson, Bunting, & McCann, 2009; Probst et al., 2006). No further sociodemographic correlate showed discriminative power in order to delineate this depressive subtype. Substance abuse/dependence was associated with the severe IARS subtype, partly fitting Rutz's male depressive syndrome (Rutz, 1999; Rutz et al., 1995). A further aspect in line with the male depressive syndrome displayed the highest relative frequencies of the masculine gender role orientation. However, as already mentioned in chapter 3.2, the overlap with Rutz's concept of male depression was only partly discernible. Furthermore, the severe IARS subtype was more strongly linked to bipolar than to unipolar depression, finally providing more clarity about the claimed differential diagnosis of this subtype (Möller Leimkühler, Heller, & Paulus, 2007). However, in analogy to the subjects fluctuating between typical and atypical symptoms, the present study

cannot ascertain if the same phenomenon applies to the severe IARS subtype in combination with one (or even more) other subtype(s). Hence, due to the lacking option to identify 'switchers', comorbidities could have been overestimated in the cross-sectional design. Nevertheless, I hypothesized higher testosterone levels for the hypomanic/manic-associated, severe IARS subtype in manuscript III. This hypothesis was based on a small number of recent studies revealing higher levels for depression associated with hypomania/mania (e.g., Johnson et al., 2013). In fact, the hypothesis was confirmed. As already described above, higher testosterone levels were also found for the severe typical subtype. Therefore, with regard to their gonadal hormone profile found in manuscript III, the two male-associated (as shown in manuscript I/II) depression severe IARS and severe typical subtypes were similar.

To summarize, the male-specific severe IARS subtype tentatively resembled Rutz's postulated male depressive syndrome (Rutz, 1999; Rutz et al., 1995). As regards the gonadal hormone associations, the severe IARS depression subtype showed significantly higher testosterone levels than the control group, and therefore was similar to the severe typical subtype.

3.3.5 Moderate subtype

As the only data-derived subtype, the highly stable, moderate group (manuscript I) showed a balanced sex proportion (manuscript I), more low-scorers (manuscript II), and a lower number of comorbid disorders for both sexes (manuscript I/ II). As mentioned in chapter 3.3.1, the initially expected higher scores for masculinity in non-severe depression subtypes (referring to the moderate subtype) could only be found for the comparison of the moderate versus the severe typical subtype (manuscript II). Furthermore, the hypothesized lower testosterone levels for moderate/mild depressive subgroups could not be confirmed (manuscript III). There are several explanations for the lacking association with low testosterone concentrations: younger age range in the current sample, variations in conceptualizing subthreshold depressive categories (DSM-categories of dysthymia or minor depression versus empirically-derived moderate subtype in the current study), and/or the missing control group in some studies. In addition, there is no international consensus on the definition of a standardized range of hypogonadism making an overall comparison of such studies difficult (Jager et al., 2013).

Combining these findings one can summarize that the moderate subtype represents a stable, valid depression subtype. However, this subtype is better characterized by its lower depression severity than by specific biopsychosocial characteristics. I speculate that this subtype is a reactive depressive subtype resulting from burden of life, which was underlined by a considerable amount of summed up critical life events (manuscript I).

Overall, the broad question can be answered by stating that particularly the empirically derived severe symptom-based depression subtypes can be quite well characterized by biopsychosocial correlates.

3.4 Mixture modelling: an appropriate statistical method in order to deal with this issue?

- *Is mixture modelling a convenient statistical approach in order to examine symptom-based depression subtypes?*

From a pragmatic point of view, mixture models, such as LCA and LTA, are simply one methodological possibility to cluster response patterns into homogeneous subgroups in available heterogeneous, categorical data. On the other hand, this statistical approach has the ability to capture the expected subtypes and, moreover, holds great explorative potential, bearing in mind the relevant theoretically background. The explorative potential of mixture models was demonstrated by the detection of two male-specific depression subtypes (manuscript II) and the identification of subtypes differing by their level of depression severity (moderate-severe) (manuscript I/II). The importance of not only relying on statistical model fit indices without considering the theoretical appropriateness of a model solution was shown in manuscript II: From a statistical perspective (i.e., model fit indices, principle of parsimony), the two-class solution seemed an appropriate model within the subsample of males. A closer examination revealed that this model solution mainly differed between low- and high scorers (for a definition see page 15 and 16). Given that there are already well-established instruments assessing the severity of depression, the additional benefits of the two-class solution were however not convincing. In contrast, the five class model showing likewise good fit indices, disclosed a severe typical and severe atypical subtype, which has been

previously characterized by biopsychosocial correlates and subtype specific treatment responses (Baumeister & Parker, 2012). The combination of this theoretical knowledge with the presence of the two further, explorative derived, male-specific subtypes led us to choose the five-class model. Consequently, it can be stated that model parsimony is not always the best imperative for an analysis.

However, despite its obvious benefits, the mixture modelling approach also exhibits model restrictions. The latent class solutions are dependent on the choice and number of indicators. For example, if further symptoms from anxiety diagnoses had been added to the indicators to DSM-criteria for MDD in the current analyses, this might have resulted in different latent classes. A further condition within mixture modelling is a large sample size. Small sample sizes with three or more classes often result in boundary estimates which may limit the model accuracy (Geiser, 2010). Finally, some authors noted that the several symptom-based subtypes display a symptom-overlap, indicating that they are not absolutely distinct from each other (Baumeister & Parker, 2012). This overlap of certain depressive symptoms is visible in the graphical symptom-profile of the subtypes. In contrast to such fuzzy subtypes, distinctive subtypes hold promise for a more detailed specification of differing entities (Ajdacic-Gross et al., submitted).

It can be concluded that, despite certain limitations, the mixture modelling approach is a beneficial statistical approach in order to capture more homogeneous subgroups in heterogeneous diagnoses such as MDD. Every statistical model has its restrictions and these can be minimized by carefully planning and performing the analyses.

3.5 A summing-up statement about the usefulness of the empirically derived subtypes and a theoretical embedding

After all these summarized findings, the following questions can be posed: What is the use of the replicated sex-related, the newly detected sex-specific and the non-sex-related depression subtypes? And how can they be embedded in the current psychopathological model of depression?
The most convincing arguments for symptom-based subtypes are the non-specific response of the heterogeneous disorder MDD to quite differing treatment modalities, and, more importantly,

response rates of antidepressants averaging only 54%, compared to 37% with placebos, and high relapse rates (Baumeister & Parker, 2012; Undurraga & Baldessarini, 2012; Vittengl, Clark, Dunn, & Jarrett, 2007). Symptom-based subtypes may improve this lack of specificity. Using the example of psychopharmacological treatment, broad action tricyclic antidepressants (TCAs) were found to be more effective in typical (melancholic) depression compared to selective serotonin uptake inhibitors (SSRIs) (Baumeister & Parker, 2012; Parker et al., 2010; Wijeratne & Sachdev, 2008). Historically, MAOIs were shown to be more effective in atypical depression (Davidson, 2007). In the meantime, its effect was found to be comparable to SSRIs, but still superior to TCAs (Baumeister & Parker, 2012; Davidson, 2007; Henkel et al., 2006). Unfortunately, clinical trials investigating modern antidepressants and their effects on depressive subtypes are still scarce, probably due to the lack of interest of pharmaceutical companies (Halbreich & Kahn, 2007). Also the effects of psychotherapies on depressive subtypes are often missing in reviews, although typical (melancholic) depression predicted poorer response to psychotherapy (Baumeister & Parker, 2012). The influence of sex has also been omitted in this area. In addition to more specific treatment, the identification of valid, homogeneous depression subtypes can facilitate communication among mental health professionals and predict clinical course (Blashfield & Livesley, 1999; McKay et al., 2004). The current doctoral thesis provides empirical findings with regard to more detailed insight in the phenomenology, biopsychosocial characteristics (including comorbidities), long-term course and transition patterns of sex-related, sex-specific, and non-sex-related depression subtypes, depicting important similarities and differences. Hopefully, that this will provide the basis for future research specifying treatment for the subjects concerned.

The converging biological-, psychological-, and social findings from the present three studies supported Engel's (1977) biopsychosocial paradigm. Each empirically derived depressive subtype was characterized by variables from one or several aspects of these three areas. However, that is actually not surprising taking into account that the biopsychosocial model is extremely broad. Although the open-minded attitude is better that dogmatism, Ghaemi (2006) criticized the eclecticism of this paradigm, in which anything goes and that has failed to sufficiently guide contemporary psychiatry. Moreover, despite some evidence in causality of biological and psychosocial processes (for example the knowledge that dysregulations of the HPA axis can determine later affective disorders; Binder & Nemeroff, 2010; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008), the still unclear interaction and linkage of the biological, psychological and social aspects are disappointing.

A somewhat more satisfactory paradigm might be the pluralism paradigm based on Karl Jaspers (1997 [1959]). On the one hand, the pluralism approach agrees with the eclectic paradigm that no single paradigm/dogma is sufficient. On the other hand, the pluralism paradigm criticizes the eclecticism because of its insufficient and confusing 'anything goes'-mentality. The pluralism model assumes that each model/paradigm has its strengths and weaknesses, and for every disease that model/paradigm is most suitable which has most strengths and fewest weaknesses (Ghaemi, 2006; McHugh, 2006; McHugh & Slavney, 1998 [1983]). Applied to the depressive subtypes and bringing together previous and current findings this would mean that for severe depressive subtypes such as atypical depression or typical depression, which are specifically linked to biological variables (e.g., BMI/testosterone levels/cortisol levels), the biological paradigm is probably most appropriate, while the moderate depressive subtype is better explained by psychosocial characteristics such as critical life events. Again, these findings underline how heterogeneous the concept of overall MDD is.

If certain disorders or subtypes would be best explained by the biological paradigm, corresponding biological correlates could indicate specific pathophysiological mechanisms. However, there are still large limitations with respect to that issue. As Allen Frances (2013a) noted, biological findings have never been robust enough to become testworthy due to the fact that within-group variability drowns out the between-group differences. Apart from Alzheimer's disease, the current research knowledge is still far away from having objective biological tests for psychiatric diagnosis and it appears quite certain that we will remain stuck with descriptive psychiatry far into the distant future. More broadly formulated, a sudden paradigm shift replacing descriptive psychopathology with an exploratory understanding of the pathogeneses of common mental disorders seems quite unlikely in the near future. Instead, this will be the gradual, painstaking work of several decades (Frances, 2013b). An inspiring and deeply influential book with regard to paradigm shifts and the development of scientific knowledge is provided by *The Structure of Scientific Revolutions* by Thomas Samuel Kuhn (1996). In analogy to examples of the Gestalt psychology, Kuhn described how the view of scientists is restricted to the current theoretical paradigm. Historically, new paradigms arose at times when more and more 'anomalies' occurred in the research progress leading to increasing discomfort (Hoffmann, 2012). Therefore, the mixture modeling approach including an exploratory strategy was a suitable method in order to enable the detection of anomalies. As examples for such anomalies I call to mind the empirically derived severe IARS depression subtype and the psychomotor retarded subtype, only partly fitting in the current conceptualization and theories. Consequently, the present

findings are hopefully an additional mosaic piece in fostering the process of a future paradigm change that will be able to explain the complex etiopathogenetical interactions between individual and environment resulting in mental syndromes and disorders.

How do the findings of this doctoral thesis correspond with the long-lasting 'splitting'-'lumping' debate about the accurately diagnostic conceptualization of depression? The data-driven methodological approach contained the potential to empirically contribute to this question. Based on the present findings I conclude that both perspectives are justified in their own specific way. The derived moderate and severe subtypes confirmed the unitarian model, which lumps depression in one single condition only varying by its severity. However, the unitarian model was not sufficient to explain the additional symptom-based subtypes, varying by partly distinct symptom patterns. Instead, these findings rather confirmed the splitting perspective. However, the binary view was again not satisfactory in order to explain the several symptom-based subtypes for both sexes. But also the conceptualization of multiple depressive disorders (Klein, 1974) was only partly appropriate because it was not able to account for the different severity levels. Cumulative evidence from research on both depression and obsessive-compulsive disorder proposed that the general unitary versus binary debate failed to consider that there is a third perspective including both dimensional and categorical aspects, therefore providing a middle ground between the 'lumping' and 'splitting' perspectives (Klein, 1974; Mataix-Cols et al., 2005; Parker, 2000). According to this model, there are certain depressive disease categories (e.g., the symptom patterns of the DSM specifiers) describable by markers, and at the same time severity differences that are sources of heterogeneity (Lamers, Burstein, et al., 2012; Parker, 2005). Hence I am in line with recent research concluding that both dimensional and categorical aspects are necessary in order to explain the heterogeneity of depression.

Hopefully, the current doctoral thesis could highlight the benefits of focusing on homogeneous MDD symptom subtypes compared to examining the highly heterogeneous disorder MDD as a whole.

3.6 Limitations

The detailed limitations of the three conducted studies can be found in the corresponding manuscripts. In the following, only the most important limitations will be briefly discussed. First, the person-centered methodological subtyping approach is simply one possible perspective on depression. But variable-centered approaches, such as regression analysis, might also have led to interesting results, e.g., by examining sex as predictor of specific depressive symptom groups. Second, the cross-sectional design of the ZInEP sample impeded evidence about the causality between biopsychosocial risk factors and depressive subtypes. Third, the small sample sizes of the psychomotor retarded subtype and certain subsamples with available hormone data restricted conclusions regarding their validity. I accommodated this point by computing effect sizes. Nevertheless, replication of the new, male-specific depression subtypes and the associations of the depressive subtypes with gonadal hormone are required. Fourth, the detected male-specific depression subtypes perhaps would have occurred analogically with higher order LCA class solutions and a larger sample size within females. Hence, replication on larger sample sizes is needed. Fifth, on closer inspection of the plotted three to five LCA class probabilities, I cannot rule out the possibility that the partitioning of the male-specific severe IARS and psychomotor retarded subtypes resulted from the severe typical subtype. The biological similarity of the severe IARS subtype and the severe typical subtype further supported the possibility that these subtypes could be conceptualized as one single subtype. However, the unequal comorbidity profiles indicated a clear difference. Sixth, due to the model-inherent characteristics of the mixture modeling approach deriving distinct subgroups of subjects, the potential overlap of the depressive subtypes in the same subject was not considered (Baumeister & Parker, 2012). Seventh, the LCA indicators were restricted to depressive symptoms and omitted anxiety and somatic symptoms due to reasons of model parsimony. This did not allow any conclusions about the female-related anxious and somatic depression (Clayton et al., 1991; Silverstein, 2002; Silverstein, Cohen, & Kasen, 2006). The inclusion of more indicators would have required much larger sample sizes.

3.7 Future directions

Based on the current findings emphasizing the heterogeneity of MDD, the future DSM classification will need revision by more accounting for homogeneous depressive subtypes. The consideration of sex as part of the DSM-text in only some groups of disorders or as MDD specifiers (Alarcon, 2009; Riecher-Rossler, 2010) is not sufficient. After further validation of the sex-related, sex-specific and non-sex-related subtypes, particularly with respect to specific treatment responses, these distinct, affective syndromes may even replace the heterogeneous diagnosis of MDD one day. Studies should focus on subjects with depressive symptoms/syndromes without having an MDD diagnosis in order to account for more flexible developments in depression research. One might imagine that many of the general current diagnostic nosologies will be reversed and clinicians and researchers will instead entirely focus on psychopathological syndromes, independently of diagnoses. For the last few years, a psychiatric development claiming such a strategy is in progress (Hoff, 2011). My hope is that more precise depression subtypes will foster the development of more personalized depression treatments.

There is a lot of work in front of us. The required number of criteria, the exact criteria and particularly the etiopathophysiological mechanisms of the depressive subtypes are still topics of discussion. Therefore, psychiatric diagnoses should rather be seen as “work in process” (Alarcon, 2009). Apart from applying statistical methods including an explorative aspect, future impetus could result from methodological strategies combining different methodological approaches (e.g., person-centered and variable-centered) when investigating a psychopathological phenomenon. This might broaden the points of view with regard to an investigated issue and prevent narrow-minded or dogmatic research attempts. Every well-performed, biological-, psychological- and social finding will display a further piece in the jigsaw of the pathophysiology and phenomenology of depression and particularly their interactions will challenge us in future. Parallelizing empirical evidence with relevant theories enables the detection of anomalies, which contain the potential to induce a paradigm change (Kuhn, 1996). However, regarding the complex psychophysiological mechanisms, we have to bear in mind the following issue: the human brain has a restricted spectrum of psychopathological expressions and for most psychopathological syndromes there is not only one specific, invariant, causal factor. The depressive syndrome, for example can be the result of a neurological disease, such as a stroke, but may also occur in reaction to a critical life event (Hackett,

Kohler, O'Brien, & Mead, 2014; Scharfetter, 2002). This has led researchers to completely change the perspective and to propose a synthesizing project positioning mental disorders along four (not necessarily mutually exclusive) etiopathic clusters: brain diseases (e.g., bipolar disorders, schizophrenia), personality-based (e.g., emotional instability), behavioral-based (e.g., alcohol consumption) or situational (e.g., grief) (McHugh, 2005). McHugh (2005) argues that the key to treatment and prognosis is not the depressive symptom but its underlying cause. Similar attempts can be found in biological psychiatry (Van Praag, 2010; van Praag et al., 1987). Suitable for all these differing perspectives and attempts, Bill Bryson (2003, p. 319) noted:

“Taxonomy is described sometimes as a science and sometimes as an art, but really it’s a battleground”.

Despite the disagreements regarding appropriate conceptualizations in psychopathological research, they all have one thing in common: the inherent human necessity to deal with the environmental complexity by performing taxonomies. The understanding of depression (and other mental disorders) remains a major future challenge. For the moment, we have to make the best of the available, phenomenological psychopathology – whatever will finally approximate most closely to the real ‘truth’ of this disorder. I sincerely hope that the ‘battle’ will pay off on a long-term basis for the actually injured, namely the individuals suffering from depression.

3.8 References

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Curriculum vitae

STEPHANIE ALEXANDRA RODGERS

PERSONAL PROFILE

Address	Florastrasse 5, 8008 Zurich, Switzerland
E-Mail	stephanie.rodgers@dgsp.uzh.ch
Date of birth	26.05.1978
Place of birth	Zurich, Switzerland
Nationality	Swiss

EDUCATION

2011 – 2014	Doctorate, University of Zurich **PhD Student, University of Zurich** Department of Psychiatry, Psychotherapy and Psychosomatics, Zurich University Hospital for Psychiatry, Switzerland Cumulative Thesis: Symptom-based depression subtypes and sex: a mixture modeling approach integrating biopsychosocial aspects Advisory board: Prof. Dr. M. Grosse Holtforth, PD Dr. phil. V. Ajdacic-Gross, and PD Dr. phil. Ch. Flückiger
2002 – 2009	Studies in Psychology, University of Zurich, Switzerland **Master of Science, University of Zurich** Specialization: Clinical Psychology Minor subjects: Psychopathology, Criminology Thesis: Suicide in the first year of widowhood: Survivalanalysis over a period of 18 years (1987-2005)
1998 – 2002	Cantonal Maturity School of Adult Education (KME), Switzerland

	Matura, Zurich, Switzerland
1990 – 1997	Rudolf Steiner school, circuit Zürichberg, Switzerland
1985 – 1990	Primary school, circuit Zürichberg, Switzerland

RESEARCH AND CLINICAL EXPERIENCE

2013 – present	Research Associate in the PsyCoLaus project (Prof. M. Preisig), Department of Psychiatry, Psychotherapy and Psychosomatics, University of Zurich, Switzerland
2009 – 2012	Research Associate in the Zurich Program for Sustainable Development of Mental Health Services (ZInEP), subproject epidemiology, Department of Psychiatry, Psychotherapy and Psychosomatics, University of Zurich, Switzerland
2006 – 2009	Postgraduated research assistant, Department of Research/Evaluation Integrated Psychiatry Winterthur (ipw), Switzerland
03/2006 – 04/2006	Clinical internship (2 month, 100%), stationary (E1), Psychiatric Hospital, University of Zurich
09/2006 – 01/2006	Clinical internship (5 months, 70%), semi-residential (Villa Klus), Psychiatric Hospital, University of Zurich

FURTHER PROFESSIONAL EXPERIENCE

1998 – 2000	Part-time work in a playgroup, Rämibühl, Zurich, Switzerland Part-time work in a pet shop, Witikon, Zurich, Switzerland Part-time work in a student hostel, Zurich, Switzerland

FURTHER INTERNSHIPS

1997	Social internship with disabled adults
	Village Aigues Vertes, Bernex-Genève, Switzerland
1996	Agricultural internship
	Hinwil, Zurich Switzerland
1994	Forestry internship
	Oberwald, Valais Switzerland
1991	Social internship with disabled children/adolescents
	Raphael school, Zurich, Switzerland

PUBLICATIONS

Publications (peer-reviewed)

Ajdacic-Gross, V., Muller, M., Rodgers, S., Warnke, I., Hengartner, M. P., Landolt, K., et al. (2014). The ZInEP Epidemiology Survey: background, design and methods. *International journal of methods in psychiatric research*.

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Muller, M., Vandeleur, C., Rodgers, S., Rossler, W., Castelao, E., Preisig, M., et al. (2014). Factors associated with comorbidity patterns in full and partial PTSD: findings from the PsyCoLaus study. *Comprehensive psychiatry, 55*(4), 837-848.

Richard, A., Rohrmann, S., Mohler-Kuo, M., Rodgers, S., Moffat, R., Guth, U., et al. (2014). Urinary phytoestrogens and depression in perimenopausal US women: NHANES 2005-2008. *Journal of affective disorders, 156*, 200-205.

Rodgers, S., Ajdacic-Gross, V., Muller, M., Hengartner, M. P., Grosse Holtforth, M., Angst, J., et al. (2013). The role of sex on stability and change of depression symptom subtypes over 20 years: a latent transition analysis. *European archives of psychiatry and clinical neuroscience*.

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Rossler, W., Ajdacic-Gross, V., Haker, H., Rodgers, S., Muller, M., & Hengartner, M. P. (2013). Subclinical psychosis syndromes in the general population: results from a large-scale epidemiological survey among residents of the canton of Zurich, Switzerland. *Epidemiology and psychiatric sciences*, 1-9.

Rusch, N., Muller, M., Ajdacic-Gross, V., Rodgers, S., Corrigan, P. W., & Rossler, W. (2014). Shame, perceived knowledge and satisfaction associated with mental health as predictors of attitude patterns towards help-seeking. *Epidemiology and psychiatric sciences, 23*(2), 177-187.

Conference presentations

Posters:

Rodgers S, Hengartner, MP, Ajdacic-Gross, V, Landolt, K, Müller, M, Kawohl, W, Rössler, W. *ZInEP – Epidemiological survey: Mental health in young and middle-aged adults in Zurich, Switzerland,* DGPPN 2010, Berlin, Germany

Rodgers S, Hengartner, MP, Ajdacic-Gross, V, Landolt, K, Müller, M, Warnke, I, Kawohl, W, Rössler,

W. *A new epidemiological survey on stress, mental health and psychotic symptoms in young and middle-aged adults in Zurich,* ECSR 2011, Berlin, Germany

Rodgers S, Ajdacic-Gross, V, Warnke, I, Müller, M, Landolt, K, Hengartner, MP, Rössler, W. *Sex-specific phenotypes of depression: preliminary results of a person-centered approach,* SPPE 2012, Basel, Switzerland

Rodgers S, Ajdacic-Gross, V, Warnke, I, Hengartner, MP, Landolt, K, Müller, M, grosse Holtforth, M, Rössler, W. *Symptom-based subtypes of depression and their psycho-social correlates: a person-centered approach focusing on the influence of sex*, IFPE 2013, Leipzig, Germany

Rodgers S, Ajdacic-Gross, Müller, M, Hengartner, MP, grosse Holtforth, M, Angst, J, Rössler, W. *The role of sex on stability and change of depression symptom subtypes over 20 years: a latent transition analysis, SPPE 2014,* Lausanne, Switzerland.

Talks:

Rodgers S, Ajdacic-Gross, V. *Epidemiologie psychischer Störungen im Kanton Zürich. Zürcher Impulsprogramm zur nachhaltigen Entwicklung der Psychiatrie ZInEP, Teilprojekt 1*.Scientific advisory council 2012, Zurich, Switzerland

Rodgers S, Ajdacic-Gross, V. *Epidemiologie psychischer Störungen im Kanton Zürich. Zürcher Impulsprogramm zur nachhaltigen Entwicklung der Psychiatrie ZInEP, Teilprojekt 1*.Scientific advisory council 2013, Zurich, Switzerland

Rodgers S, Ajdacic-Gross V, Kawohl, W, Aleksandrowicz, A, Vandeleur, V, Castelao, E, Müller M, Hengartner, MP, Rössler, W, Preisig, M. *Subtyping specific phobias and obsessive-compulsive disorders: comorbidity patterns of pure and mixed subtypes in two independent Swiss community samples.* 17th EPA Epidemiology and Social Psychiatry Meeting 2014, Ulm, Germany.

Reviewer activities

2014: Psychological Medicine
European Psychiatry
Psychotherapy Research

Zurich, 03.08.2014